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A THERAPEUTIC SCORE CARD FOR RHEUMATOID ARTHRITIS*

A Standardized Method of Appraising Results of Treatment

OTTO STEINBROCKER, M.D.,† AND ALFRED BLAZER, M.D.‡

NEW YORK CITY

CLINICAL experience and the lack of some accepted system in the literature impressed us with the need for a standardized scheme of appraising therapeutic results in chronic rheumatoid arthritis. We therefore devised the method now used in the Arthritis Clinic of Bellevue Hospital, the so-called "Therapeutic Score Card," which offers an objective and comparatively accurate method of measuring the response to therapy.

One purpose of such a scheme is, so far as possible, to divest therapeutic study of the subjective influence of the patient and of the prejudicial enthusiasm of the physician. Another is to provide a uniform method that can be employed periodically — for example, once a month — on each patient and rapidly enough to be practical and accurately enough to be reliable.

METHOD

The underlying principle of this system is to employ the chief features of rheumatoid arthritis and their response to treatment in determining the effectiveness of any therapeutic agent. To provide an accurate procedure, percentage values are accorded each of the characteristics of the disease, which are tabulated so that exact calculations can be noted and comparisons made.

The scheme is essentially a debit not a credit system. When a patient is first seen all the rheumatoid factors enumerated are noted, and for each one a debit is tabulated. This debit is actually the deduction to be made from a theoretical 100 per cent that represents the status of a recovered or healthy person. If a patient shows inflammatory swelling of the joints, a 50 per cent deduction is entered under the column entitled "Joint Swelling." If the sedimentation rate is elevated, a 15 per cent debit is recorded, and so on down the line of symptoms and signs. The patient's debits are then added across the sheet, and the sum deducted from 100. The remainder is scored in the column labeled "Total." Accordingly, a patient first seen may give a balance or total of 35 or 75 per cent, or whatever it may be, signifying a corresponding degree of freedom from rheumatoid disease. In the same fashion at regular intervals, preferably monthly, the therapeutic score is calculated.

As the treatment continues, it is possible by a glance at the record to determine the fluctuations in the patient's rheumatoid status and to discern trends toward improvement or unresponsiveness with an exactness that is calculated and not dependent to any extent on the vagaries of memory, impressions of the patient or the attitude of the observer toward the method of treatment under study. In carrying out therapeutic investigations in this disease, observations are more objective when treatment is prescribed by one person and the calculations made by another, although this method lends itself to reliable estimations by different observers owing to the standard criteria.

At the initial examination it is advisable to note detailed information on all the factors listed. This information serves as the basis of comparison from which all future estimates of progress are derived. The activity of the rheumatoid disease is then assessed and tabulated according to the severity of the features enumerated. After due deliberation we believe that the predominant clinical factors reflecting the activity and progress of rheumatoid disease are joint swelling, sedimentation rate, articular mobility, joint tenderness, weight gain (or loss), hemoglobin (or red-cell count), pain, well-being and functional capacity. Of course the selection of such factors is to some extent a matter of arbitrary decision.

After careful study of our series of rheumatoid patients the criteria were selected and given percentage values determined by much experimental calculation of the factors in the history and course. The features enumerated, we believe, offer a well

*From the Arthritis Clinic, Bellevue Hospital, Fourth Medical Division (New York University).
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†Attending physician and chief, Arthritis Clinic, Bellevue Hospital; assistant clinical professor of medicine, New York University.

‡Clinical assistant physician, Bellevue Hospital.

rounded insight into, and evaluation of, the rheumatoid status. As a matter of fact, a difference of opinion regarding the relative importance of several of these items is probably immaterial, so long as specific criteria are chosen and consistently followed throughout in all patients included in a report. The chief principle in the scheme remains that a uniform method of assay is employed and generally accepted; for such a project some criteria must be selected. Obviously the features of rheumatoid disease are not of equal clinical and pathological significance. The relative importance attached to the various characteristics is considered under the discussion of each.

Criteria of Improvement

Joint Swelling

Joint swelling is the crucial sign of the rheumatoid process.[1] Unlike tenderness, motion and pain, joint swelling is the most objective index to the patient's progress; of all symptoms, it is also the least affected by emotional influences, voluntary or otherwise. No matter how mild the condition appears or how well the patient seems to be doing, so long as any active inflammation, as evidenced by joint swelling, is present, the patient is suffering from active rheumatoid disease that may flare up at any time or assume a progressive, unfavorable course. For these reasons, before therapy is begun, an initial deduction of 50 per cent for active joint swelling under any circumstances is made. Such a debit makes it impossible for a patient to be classed as recovered or even greatly improved so long as any active articular enlargement persists.

The purpose of these ratings is usually to evaluate the effect of some remedy on the disease. From the therapeutic standpoint, the initial condition is the basis on which the maximum deduction is made.

The amount of swelling is estimated and measured, if possible, at the first examination. The joint most affected is used as the standard. When another joint becomes involved more actively, it becomes the critical one. Regardless of other signs of improvement, any degree of active inflammatory swelling of a joint remains indicative of a persistent rheumatoid process. In the presence of active articular swelling, no matter how slight, no deduction less than 40 per cent is made. Such an allowance indicates that some improvement in the swelling has occurred, but that the continuing inflammatory enlargement remains a serious indication of activity and is as likely to be associated sooner or later with a flare-up as with complete resolution. The importance attached to active joint swelling is a measure of the optimism with which results are regarded — and of their final accuracy. From that attitude, we believe, arise many of the favorable, and ultimately disappointing, opinions on various methods of treatment.

Naturally, the indurated swelling of residual postinflammatory thickening or chronic effusive synovitis must be differentiated and not accorded undue significance. Similarly, in elderly patients, cardiac or nephritic edema of the ankles and feet should not be mistaken for rheumatoid swelling. The tender lymphedema of the ankles and feet in older rheumatoid patients with varicosities and deep thrombophlebitis, as well as the postural edema of the lower extremities seen in wheel-chair patients and in those who keep their feet over the edge of the bed for long periods, must be recognized.

Erythrocyte Sedimentation Rate

This test is accorded a debit of 15 per cent when sufficiently elevated. The sedimentation rate thereby receives a higher rating than the remaining rheumatoid features. In estimating the significance of the sedimentation rate, we have borne in mind the difference of opinion regarding both the interpretation of a persisting increase in apparently recovered patients and the importance of this test compared with joint swelling and other characteristics of the disease. The use of the score card in our series of cases indicates that the sedimentation rate has been given a place proportionate to its clinical role.

Rates of 15 mm. by the Cutler method and 25 mm. by the Westergren are taken as bases. In other words, if a patient first exhibits an increased rate at or above those points 15 per cent is deducted. In the course of time if the rate goes above these levels, no further deduction is made, because the total debit possible for abnormality of erythrocyte sedimentation is already represented. If the rate later drops, all or part of the 15 per cent is allowed in proportion to the decrease from the original high.

If the record at first shows a sedimentation rate of 75 mm. (Westergren method) and a rate of 50 mm. at the next determination, 7.5 per cent is allowed for the improvement so that the score card then registers a deduction of 7.5 instead of the original 15 per cent in that column. The scoring can be scaled according to the same principle for sedimentation rates performed by other technics.

In the rare cases in which the patient has a normal sedimentation rate to begin with, in the presence of definite clinical signs of rheumatoid activity, no debit is charged for the test. Similarly, when the patient completes treatment and the normal rate remains unchanged, no allowance or deduction is made. In fact, none of the initially normal elements of rheumatoid activity that remain unaltered enter into the calculations. Thus, such signs do not in any way influence the estimate of the patient's response to treatment, which is based on the other abnormal factors manifested. If, on the contrary, a patient appears with a normal sedimentation rate in the presence of other positive signs and finally shows no response to treatment and still presents an elevation of the sedimentation rate at the last examination, the 15 per cent is, of course, charted

to increase the total debit and to show that the patient's condition is worse, at least to the extent indicated by the elevated rate. These are commonsense applications of the same principle and are readily acquired by repeated interpretation of the clinical picture in these arithmetical terms.

Joint Motion

Joint mobility is given only one twentieth of the significance of the over-all picture — in other words, 5 per cent. Although articular motion occupies an important place in the activities and in the improvement of the patient, the joint inflammation that is usually present so frequently determines articular function that motion is regarded as secondary. At times patients with rheumatoid activity without demonstrable joint swelling suffer some disability. The safer emphasis is considered to be on joint swelling, without completely ignoring joint motion. The improvement of joint mobility, which is rated according to its progress from the original limitation, goes from a debit of 5 per cent to 0 if complete motion is restored, or any part of 5 per cent dependent on the degree of recovery of function.

In severe rheumatoid disease, limited motion or ankylosis is sometimes due to fixed and irreversible changes, such as destruction of cartilage, fibrous or bony ankylosis and subluxation. Naturally, the rheumatoid status should not be discredited because of these conditions. Even if medical treatment is effective, it can only arrest the activity of the disease and cannot improve the irreparable changes and resulting loss of function.

Joint Tenderness

Joint tenderness, like joint mobility, is usually so intimately associated with articular swelling and inflammation in rheumatoid disease that a distinction is almost superfluous. There are patients without definite joint swelling, however, who present joint tenderness as the earliest symptom. There are others in whom the joint swelling has disappeared and whose only evidence of articular involvement is the tenderness elicited by palpation. In such cases slight or great additional features of rheumatoid activity are apparent. So long as the periarticular tenderness persists (especially when compared with palpation of the opposite or other normal or recovered joints), it is best regarded as a sign of continuing activity and given a debit of 5 per cent if unchanged, or any proportion thereof in relation to the initial tenderness. Of course it is essential to distinguish the soreness due to post-rheumatoid periarticular thickening or fibrositis that may no longer signify rheumatoid activity but secondary terminal changes.

Spindle-shaped joints are pathognomonic of rheumatoid arthritis. In some cases, of course, even after the disease is arrested the spindle-shaped deformity persists. The tenderness about such joints must be carefully evaluated to rule out irreversible periarticular changes as the source of the soreness. If the other signs of rheumatoid activity have resolved, it is safe to assume that in all likelihood the soreness is due to secondary changes. When tenderness continues unduly as a lone symptom, emotional factors must be evaluated. Generalized hyperesthesia should be excluded. Occasionally the previously involved joints become the outlet for psychogenic disorders, complicating the chronic picture and clouding the signs of recovery even after objective signs have disappeared. Pseudoankylosis may be simulated by the same factors, particularly by fear of using joints previously painful on motion.

Hemoglobin

A lowered hemoglobin level is characteristic of most patients with active rheumatoid disease. It becomes, therefore, a fundamental feature of the rheumatoid process. The upper normal value is considered to be 13.5 gm. per 100 cc. (85 per cent). The hemoglobin is charted at the first examination. If it is above 80 per cent it is considered normal; if it is below 80 per cent, a deduction of 5 per cent is made. If the hemoglobin rises during the course of treatment, a portion of this 5 per cent is reduced according to the degree of improvement toward the normal base. If the hemoglobin remains unchanged at the end of treatment, the same debit is charged, influencing the record of the over-all response of the patient.

Weight Loss

Weight gain is widely accepted as proof of improvement in the patient's general condition when accompanied by other evidence. Avoirdupois alone is no measure of a satisfactory state, because many patients with active rheumatoid arthritis are overweight. In the usual, asthenic, underweight subject, however, weight gain can well be used as a gauge of response to treatment. In such an underweight patient, provided weight loss has already been noticed during the period of illness, a debit of 5 per cent is made at the outset of treatment. If the patient later shows a gain of more than 1 pound, proportionate credit is given up to recovery of the average weight before illness, which rates a full allowance of 5 per cent.

Pain

Pain represents one of two symptoms included in the score sheet that are purely subjective and in their entirety are given 10 per cent, or one tenth, of the over-all significance of symptoms and signs. Subjective factors are intentionally relegated to a minor place, because they are regarded as the most misleading items in any attempt to arrive at an accurate evaluation of therapy, and are included only because of their widespread use in the literature. To exclude them would probably delay general ac-

ceptance of a standardized method of evaluating therapy. There are enough objective features of rheumatoid disease, as shown in the score card, to guide the assay of any method of treatment without depending too much on the patient's reactions. It is obvious that when joint swelling is improved, joint motion and tenderness ameliorated, relief of pain and a greater sense of well-being almost invariably follow. We have compromised, nevertheless, to the extent that largely subjective responses to treatment are allowed 10 per cent, half of which is allotted to pain.

Even pain can be placed on a more or less objective basis if the patient is initially instructed to take some analgesic, such as aspirin or another salicylate. Some patients are so resigned to their chronic ailment that they prefer to be stoical; in such cases it is gently but firmly insisted that they take medication in adequate doses for relief of pain. In that way, the number of salicylate tablets required daily in the course of time serves as a somewhat objective estimate of the intensity of pain. The initial 5 per cent debit can be scaled down in proportion to the lessening of pain. Loss of sleep due to pain also throws a revealing light on its severity: if insomnia is eliminated, at least half the original debit is canceled. The patient's emotional make-up is important in the evaluation of subjective factors, and the examiner must be guided accordingly. The trend of pain response over a period must be taken, and the transient influence of weather and humidity discounted.

Well-Being

The well-being of the patient, which represents an estimate of general subjective response to treatment, includes such factors as mental attitude, loss of anxiety, cheerfulness, confidence, desire to return to some or all of the previous duties and renewed interest in various social activities. Also included are a variety of minor symptoms, which are more or less dependent on some of the features already described and are mentioned merely to outline the scope of this symptom, such as increased appetite, reduced or absent sensations of chilliness and vasomotor disturbance. The interpretation of this phase of the clinical picture depends greatly on the sound judgment of the observer. It is so lacking in objectivity and so reliant on many intangible factors in one way or another that it is allowed only 5 per cent.

Functional Status

The functional status of the patient, to a variable extent, reflects fluctuations in the rheumatoid condition. When increased function arises directly from resolving articular inflammation, the change is adequately registered by improvement in swelling, tenderness and motion. For that reason only 5 per cent is allowed for this feature.

Functional capacity — use of the joints and ability to perform necessary duties or to work — does not necessarily parallel the degree of rheumatoid activity. Few patients whose rheumatoid process becomes inactive fail to acquire greatly enhanced function, unless severe and irreversible joint changes have occurred. Frequently, however, patients under treatment show increased joint function and capacity for work with little or no improvement in the chronic joint inflammation. In fact, some patients with severe rheumatoid polyarthritis continue to work despite pathologic changes and disability far greater than those of others who are incapacitated. The personal equation and many socioeconomic and psychologic factors determine these contradictory manifestations.

The ideal in the therapy of rheumatoid disease would be achieved by the complete arrest of pathologic activity and the physical, economic and social rehabilitation of the patient. Such a goal would often embrace two separate problems: the arrest of rheumatoid activity and the restoration of function or work capacity. The real effect of a specific therapeutic agent must be judged by its influence on the rheumatoid process. The increase of functional capacity cannot be attributed entirely to such a remedy unless the signs of rheumatoid activity are proportionately improved or abolished. This distinction is often overlooked in evaluating the results of a drug.

The enthusiastic atmosphere surrounding the initiation of some new method of treatment often temporarily stimulates functional capacity without materially influencing the pathognomonic features of the disease. Increased locomotion effected by any means is naturally welcome but is not retained unless the underlying inflammation has simultaneously been suppressed. Functional capacity usually represents the effect of the whole therapeutic program, including many helpful measures not directly influencing rheumatoid activity, such as physical and occupational therapy, orthopedic aids, analgesics, and the psychologic forces, especially the patient-physician relation. In judging the result of any specific treatment or adjunct, one should therefore regard increased function as subsidiary to the progress of the characteristic signs, as in the score card.

Classification of Response

The chief purpose of the therapeutic score card is to arrive at total values that determine whether the patient is to be classified as apparently arrested, greatly improved, slightly improved or unimproved (or worse). After the patients are classified according to their scores, the results of scoring in each case are compared with an estimate previously made from knowledge of the patient and from the progress notes. From this comparison categories of response can be classified reliably according to the percentage

made on the score card. The disease is apparently arrested when the score totals 76 per cent or more; a total of 51 to 75 per cent indicates great improvement; 26 to 50 per cent slight improvement; and less than 25 per cent no improvement.

Table 1 presents the score cards of 4 cases of rheumatoid arthritis, which are briefly described below. The salient features of each case are easily noted by reference to the score card. Patients representing each type of response are included to illustrate their classification in the various categories.

TABLE 1. *Therapeutic Score Cards of 4 Patients with Rheumatoid Arthritis.*

Case No.	Date	Debits									Total (100 minus Debits)
		Joint swelling	Joint motion	Joint tenderness	Erythrocyte sedimentation rate	Hemoglobin	Weight	Pain	Well-being	Functional capacity	
		%	%	%	%	%	%	%	%	%	%
1	11/23/43	50	5	5	0	0	0	5	5	5	25
	8/18/45	0	0	0	0	0	0	0	0	0	100
2	11/23/43	50	5	5	15	0	5	5	5	5	5
	8/3/45	40	0	0	0	0	0	0	0	0	60
3	11/23/43	50	5	5	15	0	5	5	5	5	5
	8/18/45	40	3	3	15	0	0	3	3	3	30
4	10/13/43	50	5	5	15	0	0	5	5	5	10
	8/25/45	45	5	5	15	0	0	5	5	5	15

CASE 1 (score-card status: arrested). P. H., a 52-year-old man, was seen with slowly progressing early rheumatoid arthritis of 8 months' duration. On November 23, 1943, at the beginning of gold therapy, physical examination showed moderate swelling of the metacarpophalangeal joints of both hands, stiffness and tenderness at these joints and limitation of joint motion. Cystic tendonitis, with tenderness, was also noted. The average weight was 180 pounds, and there had been no weight loss. There was a subjective complaint of moderate pain. The patient was uncomfortable but stoical; he had been unable to work for the last 8 months. The erythrocyte sedimentation rate was 8 mm. (Cutler method), and the hemoglobin 90 per cent. Gold therapy was completed on July 15, 1944.

Examination on August 18, 1945 revealed no joint swelling, full joint motion and no pain or tenderness. There was no change in weight, and full functional capacity was indicated by the fact that the patient had returned to work at his previous job. The erythrocyte sedimentation rate was 7 mm. (Cutler method), and the hemoglobin was 90 per cent.

CASE 2 (score-card status: greatly improved). C. C., a 49-year-old woman, had had active, moderately advanced rheumatoid arthritis with a fluctuant course for 12 years. On November 23, 1943, at the beginning of gold therapy physical examination disclosed swelling of both wrists and metacarpophalangeal joints and of both knees. There were limitation of joint motion and tenderness and severe pain on motion. The patient who weighed 114 pounds, had lost weight, and her general physical condition was poor. She was able to do only light housework. The erythrocyte sedimentation rate was 23 mm. (Cutler method), and the hemoglobin was 13.8 gm. Gold therapy was completed on January 13, 1945.

On August 3, 1945, joint swelling had decreased but slight swelling was present. There was no limitation of joint motion or tenderness. The erythrocyte sedimentation rate was 12 mm. (Cutler method), and the hemoglobin was 14 gm. The weight was 128 pounds. The patient's general physical condition was excellent, and she was able to do full work.

CASE 3 (score-card status: slightly improved). C. S., a 34-year-old woman, had had ambulatory, active, advanced rheumatoid arthritis for 13 years. On November 23, 1943, physical examination at the start of gold therapy revealed swelling of both wrists and the metacarpophalangeal and interphalangeal joints. Both knees and ankles were involved, with much periarticular swelling, and there was limitation of joint motion, as well as tenderness and pain on motion. A flexion deformity of the right hip joint was noted. The erythrocyte sedimentation rate was 20 mm. (Cutler method), and the hemoglobin 13.1 gm. The patient weighed only 102 pounds and complained of severe pain and pain insomnia. She was depressed and felt weak. Her functional capacity was limited to self-care. Gold therapy was completed on January 13, 1945.

On August 18, 1945, inflammatory joint swelling had decreased but was still present. Joint motion had improved about 40 per cent, and joint tenderness had decreased about 40 per cent. The erythrocyte sedimentation rate was 23 mm. (Cutler method), and the hemoglobin 13.3 gm. The patient had gained 28 pounds. The pain was less severe, and she was able to sleep with less aspirin. Her general outlook was better and she enjoyed food. Functional capacity was limited to light work.

CASE 4 (score-card status: unimproved). B. H., a 58-year-old woman, had had active, early rheumatoid arthritis for 3 months. On October 13, 1943, at the start of gold therapy, physical examination showed swelling of both wrists and metacarpophalangeal joints and swelling of both knees and ankles. There was limitation of joint motion, as well as tenderness and pain on motion. There had been no weight loss, the average weight being 152 pounds. Pain was severe, with pain insomnia. Her general physical condition was poor, and functional capacity was limited to light housework. The erythrocyte sedimentation rate was 25 mm. (Cutler method), and the hemoglobin 85 per cent. Gold therapy was completed on October 28, 1944.

On August 25, 1945 swelling of both wrists and metacarpophalangeal joints had decreased, as had the swelling of both knees. There was no swelling of the ankles. Limitation of joint motion and joint tenderness were unchanged. The erythrocyte sedimentation rate was 25 mm. (Cutler method), and the hemoglobin 13.5 gm. The average weight was still essentially the same, and severe pain, with insomnia, was present. General physical condition was still poor, and functional capacity was unchanged.

OTHER FEATURES

Some characteristics of rheumatoid arthritis that are important in the diagnosis or progress of the patient have not been included among the features used for estimating response to therapy because they were not sufficiently informative for our purposes, or because they could only supply overlapping evidence already derived from other items in the score card.

The signs that are especially typical of acute and subacute rheumatoid arthritis need no discussion, because our subject is chronic rheumatoid arthritis. A low-grade fever and tachycardia, which are sometimes noted in the course of active, chronic rheumatoid arthritis, are so characteristic of a florid rheumatoid process that they are usually accompanied by definite joint swelling as a more important guide to the patient's progress. In themselves these signs are not sufficiently specific for precise evaluation when they arise as prodromal symptoms of a flare-up in an apparently arrested patient. They merely signalize the probability of an impending relapse requiring close observation and treatment. The characteristic joint swelling of some degree ordinarily appears soon enough to serve as the chief guide to the response to treatment.

Muscle atrophy is usually a sign of advanced arthritis, either active or burnt out. The former process, in which muscle wasting and weakness are secondary manifestations of inflammation, disuse and trophic disturbances, is one of the late signs. Shrinking of muscle is often associated with, but does not give positive evidence of, rheumatoid activity, nor does the degree of atrophy parallel the severity of the activity with which it is allied. When the inflammation subsides, muscle wasting is likely to improve, partly or completely as a result of the abolition of pain, spasm and disability. The lag in muscle recovery, however, is apt to take so long after improvement or arrest of rheumatoid activity that it cannot serve as a practical index to therapeutic response.

Subcutaneous nodules, ganglions (tendon cysts), synovial swelling, nodular tendonitis and tenosynovitis are frequent manifestations of rheumatoid activity. They have not been tabulated in a special column, because they are usually associated with joint swelling and constitute a variation, or additional evidence, of soft-tissue inflammation. Such signs represent invasion of extra-articular, juxtaarticular or periarticular structures by the rheumatoid process. Occasionally any of these pathologic changes precede definite joint swelling, persist after joint involvement is no longer discernible, or crop up when the clinical features appear to be improving. In many such cases these symptoms must be interpreted as evidence of rheumatoid activity equivalent to joint swelling and charted accordingly.

Roentgenologic changes offer definite aid in the diagnosis and in the grading of rheumatoid arthritis. When activity diminishes or subsides the x-ray pictures of the joints are slow to reflect the improvement in the articular structures for so long a period that they rarely give assistance in the evaluation of response to therapy that is not adequately provided by clinical signs.

The demonstration of streptococcal agglutinins in the blood serum is regarded as strong evidence of activity.[2] The facilities for this test are limited to so few observers that it has been omitted from the score card.

There are other clinical findings, such as lymphadenopathy and splenomegaly, to mention only a few, that are not included. They are encountered too infrequently and their relation to the progress of these patients is too indefinite to warrant special consideration.

Of course, no mechanical scheme for rating the response of patients can be altogether perfect. The yardstick expounded recently by Bayles and Hall[3] offers an excellent method of accurately assaying therapy. At times cases that completely defy accurate classification are encountered. According to our experience the number is likely to be small and negligible when a standardized method is employed in a large series of patients.

Summary

The therapeutic score card provides a simple method of charting the effects of treatment on the main features of each patient's rheumatoid arthritis. The total progress, if any, can be summarized readily by the changes reflected in the chief characteristics of the clinical picture. This scheme affords a uniform method of assaying by definite standards a patient's initial condition and later course under therapy. The final classification into degrees of response provides a universally understandable and comparable set of criteria.

Reports based on some such method of scoring, even when derived by different observers, furnish a more consistent and easily correlated pool of information for the evaluation of therapeutic agents than is now available. The following benefits would accrue from the use of an accurately tabulated system embodying certain uniform standards and procedures: specific indexes of rheumatoid activity; assessment of the influence of treatment by the effect on such indexes; uniform rating of total results according to a sliding scale described; and use of an identical nomenclature for the various degrees of response.

References

1. Steinbrocker, O. *Arthritis in Modern Practice: The diagnosis and management of rheumatic and allied conditions.* 606 pp. Philadelphia: W. B. Saunders Company, 1941.
2. Cecil, R. L. Necessity of certain criteria for diagnosis and cure of rheumatoid arthritis. *Ann. Int. Med.* 11:637-642, 1937.
3. Bayles, B., and Hall, M. G. Yardstick for rheumatoid arthritis applied to patients receiving gold-salt therapy. *New Eng. J. Med.* 228:418-421, 1943.

CHIARI'S SYNDROME*

Report of a Case

HAROLD L. HIRSH, M.D.,† AND BENJAMIN MANCHESTER, M.D.‡

WASHINGTON, D. C.

CHIARI'S syndrome is a rarely observed clinical entity and is seldom diagnosed during life. It was first adequately described by Budd[1] in 1846 but bears the name of Chiari,[2] who in 1899 reported more completely 3 cases seen in his clinic and collected 7 additional cases. As first described the syndrome was a manifestation of a primary obliterating endophlebitis of the hepatic veins. Other related pathologic processes have subsequently been shown to produce this disease entity.

The symptom complex manifested by this syndrome is not generally known. A search of the literature reveals only about 70 reported cases. Out of 11,979 autopsies at the Stanford Department of Pathology since 1898, only 5 cases were found, an incidence of 0.42 per cent.[3] At the Mayo Clinic, from 1910 to 1939, Kelsey and Comfort[4] found 20 cases. The syndrome occurs in all ages and with equal frequency in both sexes. Over 50 per cent of the cases reported occurred in patients between the ages of twenty and forty-years,[5–7] although the range was between seventeen months and seventy years.

The clinical picture of Chiari's syndrome, which is clearly illustrated by the following case report, is of special interest since the diagnosis was made before death.

CASE REPORT

R. B., a 24-year-old Negro, was admitted to Gallinger Municipal Hospital on December 24, 1943, complaining of increasing weakness, faintness and weight loss for the previous 6 months. During the period of his present illness he had consulted several physicians, and numerous nontoxic medicaments had been prescribed without avail. The patient admitted consuming about a quart of whiskey daily during the preceding 6 months. He had worked as a laborer first in a printing establishment and more recently in a steel mill. The remainder of the history was not remarkable except that he had eaten clay as a child. He denied any knowledge of venereal infection or treatment with any drugs known to be toxic.

On admission the temperature was 100°F., the pulse 100, and respirations 28. The blood pressure was 130/80. In addition, marked pallor, dental caries and generalized lymphadenopathy were noted. The heart was not enlarged, and there were no thrills or shocks. The heart sounds were of good quality, with a regular rhythm; the aortic 2nd sound was greater than the pulmonic. A soft systolic murmur was audible over the precordium, loudest at the apex and not transmitted to the axilla. The lungs and abdomen were normal.

Laboratory studies revealed the presence of a marked normocytic, normochromic anemia, as demonstrated by a red-cell count of 1,500,000, with 3 gm. of hemoglobin. The white-cell count was 2500, with 38 per cent lymphocytes, 30 per cent band neutrophils, 27 per cent segmented neutrophils, 4 per cent metamyelocytes and 12 per cent mononuclear cells. The platelet count was 146,000; the reticulocytes numbered 5 to 7 per cent. A Kahn test, a blood culture, the blood urea nitrogen, and urinalysis were normal. Twenty per cent sickling was noted in a 24-hour incubated specimen. The icterus index was 5.

The diagnosis was normocytic, normochromic anemia of unknown etiology.

A week after admission the patient manifested a painful swelling of the right leg that subsided during the following 2 weeks. During this time and for the next 2 weeks the temperature ranged between 100 and 103°F., and the pulse between 80 and 110. The physical findings remained essentially the same as on admission. The patient was given whole-blood transfusions, ferrous sulfate, vitamins and symptomatic measures, with improvement in the general condition and blood picture. The red-cell count rose to 2,530,000, with a hemoglobin of 7 gm., and the white-cell count to 5000, with 29 per cent lymphocytes, 2 per cent monocytes, eosinophils and basophils and 14 per cent band and 51 per cent segmented neutrophils. Meanwhile, studies were undertaken to ascertain the cause of the anemia. X-ray films of the chest, gastrointestinal tract, skull and long bones were entirely negative, as were regular and multiple precordial lead electrocardiograms. Examination of the stools for ova, parasites and blood was completely negative. Repeat blood cultures, blood urea nitrogen levels, various agglutination tests, icterus indexes, stool examinations and urinalyses continued to show no abnormality. The Frei skin test was negative. A first-strength tuberculin skin test was positive.

Two months after admission, a septic temperature developed. The patient appeared gravely ill and complained of abdominal pain, with generalized tenderness and distention. After a few days, he developed diarrhea, which showed no unusual bacteriologic findings but resisted all treatment. A week following the onset of these complaints he developed signs of thrombophlebitis of the left lower leg. Edema of the extremity advanced to involve the scrotum and penis and later the right lower leg. In the interim the liver became enlarged, ascites developed, and a distinct abdominal and thoracic venous pattern appeared. The venous pressure was markedly elevated in the lower extremities and normal in the upper extremities. The general condition became worse; examination of the blood revealed an anemia and leukopenia as severe as that on admission. The venous disease was treated symptomatically, and the previously described supportive measures were continued.

Two weeks after the development of thrombophlebitis chest pain, cough and hemoptysis, with no pulmonary signs, appeared. X-ray examination of the chest showed evidence of a small pulmonary infarct of the right upper lobe and thickened pleura at the right base. Other studies were repeated and were still within normal limits. In April, shortly after the pulmonary infarction, the patient began to improve. Examination of the blood showed a red-cell count of 2,800,000, with 8.5 gm. of hemoglobin, and a white-cell count of 6200. Liver-function studies, including repeated hippuric acid synthesis, bromsulfalein and cephalin flocculation tests, were normal. Examination revealed evidences of thickened pleura at the right base, hepatomegaly (1 fingerbreadth below the costal margin) and minimal edema of the ankles. The last 2 months of hospitalization were relatively uneventful except for the development of a lymph-node abscess in the right axilla, which was incised and drained, and a bout of sickle-cell crises, with a decrease in the number of cells, a reticulocytosis of 11 per cent, slight jaundice and increased urobilinogen in the urine. These were minor incidents and apparently had no effect on the course. The patient was discharged on May 17, with diagnoses of thrombosis of the inferior vena cava, Chiari's syndrome and normocytic, normochromic anemia of undetermined etiology.

*From the George Washington Medical Division, Gallinger Municipal Hospital, and the Department of Medicine, George Washington University School of Medicine.

†Clinical instructor in medicine, George Washington University School of Medicine.

‡Associate in medicine, George Washington University School of Medicine.

The patient was to be followed as an outpatient. He returned once for a check-up several weeks after discharge. The findings were unchanged. He was readmitted on June 29, 1944, complaining of fatigue, nervousness, weakness, pains in the wrists, fever and symptoms of an acute upper respiratory infection. Examination revealed a temperature of 102°F., a pulse of 110, an icteric tint to the scleras and skin, pallor, generalized lymphadenopathy, retinal hemorrhages, scattered rales in the left base, moderate cardiomegaly, a precordial (Grade I) blowing systolic murmur, hepatomegaly (1 fingerbreadth below the costal margin) and minimal ankle edema. Examination of the blood showed a red-cell count of 660,000, with 3 gm. of hemoglobin, and a white-cell count of 3000, with 40 per cent lymphocytes, 6 per cent mononuclear cells and 7 per cent band and 47 per cent segmented neutrophils. Urinalysis and a Kahn test were negative. The patient was given transfusions and other supportive and symptomatic measures, but he continued to decline and died on the 5th hospital day with essentially no change in the findings. The terminal event was characteristic of a pulmonary infarct.

Autopsy. Gross examination revealed a yellow tinge to the skin and scleras. Six hundred cubic centimeters of clear straw-colored fluid was present in the chest on the right and 1000 cc. on the left, and 800 cc. of fluid was found in the peritoneal cavity. In the pericardial sac there was 100 cc. of similar fluid.

The liver was 4 cm. below the costal margin. There were a few adhesions between the spleen and surrounding tissues. The liver was smooth, congested, swollen and extremely firm. On cut section there were marked congestion and an irregular yellowish area suggesting fatty degeneration. When the hepatic veins were opened partially organized clots, firmly adherent to the vessel wall, were found. On microscopic examination the liver showed tremendous destruction, hemorrhage and congestion. The bile ducts were dilated and filled with bile. There was thrombus formation in many veins, and periductal fibrosis was marked.

The right lung weighed 725 gm., with roughened pleura over the right upper lobe. The right upper lobe showed increased consistence, and a cavity 2 cm. in diameter, surrounded by caseous material, was found in the substance of this lobe. A few calcified nodules were found in the right lower lobe, in addition to areas suggesting old infarcts. The left lung weighed 640 gm. and showed areas of old and new infarcts in the lower lobe. Microscopic sections of the lungs revealed the alveoli filled with granular debris in which occasional ghostlike outlines of phagocytic cells were seen. Inflammatory cells surrounded the alveoli. Another section showed an organized thrombus, with fibroblastic proliferation in the surrounding tissues.

The heart weighed 380 gm. There appeared to be slight dilatation of the left ventricle. The endocardium was intact. Slight fibrosis and edema were noted on microscopic examination.

The spleen weighed 455 gm. The capsule was smooth and tense, except at the site of adhesions. On section, the pulp was deep pink, with a firm, almost rubbery consistence. There was a blurred appearance to the architecture. A few small, grayish-pink, round areas were present, suggestive of tuberculous nodules. The structural detail was lost in the infarcted area, which was surrounded by a zone of hyperemia, with diffuse reticular fibrosis. The malpighian nodules were less numerous and conglomerate than those usually seen.

The pancreas, gastrointestinal tract, aorta, adrenal glands and the genitourinary system, including the kidneys, prostate and bladder, were normal.

The inferior vena cava was thickened and narrowed. A dense, firm band formed most of the posterolateral wall. There were adherent patches in its upper portion. It was completely blocked about 2.5 cm. below the renal vein where there was an organized, grayish-white, firm thrombus. Similar thrombi were found in the femoral veins. The azygos system was markedly dilated.

The anatomic diagnoses were thrombophlebitis of the hepatic veins, thrombosis of the inferior vena cava, lung abscess of the right upper lobe, multiple pulmonary infarcts, pleural and pericardial effusion and splenomegaly.

Discussion

The case presented above is one of the few reported in which the diagnosis of Chiari's syndrome was made during life. The development of abdominal pain, hepatomegaly, splenomegaly and ascites superimposed on peripheral edema as a result of peripheral thrombophlebitis made the diagnosis likely. This impression was confirmed at autopsy. This is a case of the chronic form of the syndrome in which prolonged survival was possible. The thrombosis was gradual; the occlusion was incomplete, and recanalization sufficient to allow for adequate collateral circulation and the re-establishment of biliary blood flow.

This syndrome may be due to primary disease of the hepatic venous system or secondary to disease in other parts of the body. Originally it was described as a primary endophlebitis of the veins of the liver.[8] Simple thrombosis of the inferior vena cava above the entrance of the hepatic veins, with or without involvement of these veins, has also been shown to be responsible for this syndrome. Such thrombosis is frequent in the presence of inflammatory changes in the inferior vena cava,[9, 10] although Thompson and Turnbull[11] consider the inflammatory changes secondary to the thrombosis. The two processes are often associated and aid in the propagation of one another. It has been postulated that the entrance of the hepatic veins into the inferior vena cava provides a selective site for thrombosis because of the eddy currents formed at the oblique angle at which the hepatic veins empty into the vena cava.[12–14] Torsion on the hepatic veins by the liver when in the upright position, causing mechanical damage and scar tissue occluding the veins, has been suggested as another mechanism favoring the production of thrombosis in the hepatic veins.[15] Still another theory proposes that the venous thrombosis results from the retardation or even reversal of flow of venous blood at the diaphragmatic opening of the inferior vena cava as a result of increased intrathoracic pressure on inspiration. Several hypotheses favoring a congenital etiology have been advanced. Rosenblatt[16] believed that the etiology could be fibrosis following a fetal interstitial hepatitis occluding the hepatic veins or preventing their union with the inferior vena cava. Moore[17] suggested that there might be a patent ductus venosus that, as a result of some irritant, began to obliterate and extended to involve the hepatic veins. Another possibility is that the intrauterine process of obliterating many of the venae revehentes progresses too far.[18] A congenital stricture at the point of junction of the hepatic veins and inferior vena cava has also been suggested.[19]

Intrahepatic and extrahepatic causes have been described as causing thrombosis of the hepatic veins. Rolleston and McNee[20] believe that the condition is always secondary — it is frequently secondary to disease elsewhere in the body. Alcoholism,[1] syphilis,[2, 21] pregnancy[11] and chronic cough[6] have been described as predisposing factors. Of the intrahepatic causes, tumors,[3, 14, 22] cirrhosis,[4, 18, 22–24]

gummas,[2, 4] hydatid cysts,[5, 24] abscesses,[4, 24] hepatitis[16, 19] and perihepatitis[24] have been described. The mechanism responsible for thrombosis of the hepatic veins is thought to be due to pressure or injury to the veins, causing narrowing of the lumen and slowing of the circulation. Schüppel[25] was of the opinion that increased coagulability of the blood was necessary before thrombosis occurred. Many extrahepatic causes have been reported: pancreatic cysts and enlarged peritoneal lymph nodes,[24] nonspecific inflammatory masses,[24] anomalies,[6, 12] trauma,[6, 15] scars,[20] acute or chronic constrictive pericarditis,[11, 13] tumors,[3, 4, 24] metastatic carcinomatous invasion or thrombosis of the inferior vena cava,[3, 26] malignant or infectious emboli,[20] thrombophlebitis migrans,[12] local[5] and general infection[3, 13, 27, 28] and polycythemia rubra vera.[25, 28–35]

The association of Chiari's syndrome and sickle-cell anemia in the case reported above aroused interest in the relation between the two diseases. A review of the literature failed to disclose a case of Chiari's syndrome secondary to sickle-cell anemia. It is well recognized that thrombotic episodes occur frequently in patients with this type of anemia, particularly while the patient is in a crisis. Although such episodes in this case did not occur during an exacerbation of the sickle-cell anemia, the development of widespread thrombosis in a patient with this disease is highly suggestive.

The clinical features of this syndrome vary, depending on whether the acute or chronic type is involved and on whether the occlusion is partial or complete and whether recanalization occurs. Hess[6] in 1905 and Thompson and Turnbull[11] in 1912 elaborated on the clinical aspects of the syndrome. The acute form, which results from a sudden obstruction of the outflow of hepatic venous blood, is manifested by abdominal pain, frequently over the liver and radiating to the back and shoulders, as well as by nausea and vomiting. On examination there is abdominal guarding, rapid, tender enlargement of the liver, splenomegaly on occasion and ascites. Sometimes the patient becomes delirious and comatose and finally goes into shock. Death invariably results in one to four weeks, unless the obstruction is incomplete or recanalization occurs. Jacobson and Goodpasture[14] reported a case in which the patient developed sudden swelling of the liver and acidosis superimposed on signs of inferior vena cava obstruction, indicating occlusive involvement of the hepatic veins.

In the chronic form there is either gradual occlusion of the venous drainage of the biliary system or repeated thromboses in small vessels. The patient develops gastrointestinal symptoms consisting usually of indigestion, epigastric pain, nausea and vomiting. There is gradual enlargement of the liver, occasionally splenomegaly, ascites that reaccumulates rapidly and resists diuretics, a venous pattern on the abdomen and thorax, edema of the lower extremities and, rarely, cyanosis and jaundice. Hoover[13] reported a case in which findings did not appear until the occlusion was complete. Low-back pain attributed to congestion of the kidney has been reported as a prominent symptom.

It was postulated by Hutchison and Simpson[18] that the ratio of collateral circulation to circulation lost by obstruction determines the severity of the symptoms and signs experienced by the patient. Collateral circulation occurs more frequently when the obstruction is gradual than otherwise. In the chronic form there is eventual development of delirium and coma as a result of liver failure. Death invariably occurs in six months, or at the most in several years[23, 36] and is preceded by signs of liver failure, the hepatorenal syndrome[37] or renal failure.[14, 24] Continued life is possible in limited thrombosis, incomplete occlusion, early recanalization or development of adequate collateral circulation. Hutchison and Simpson[18] reported a case in which the patient lived for twenty-five years with manifestations of this syndrome, dying only as a result of a laparotomy. Other cases with prolonged survival in which autopsies were not done have been described.

Thompson and Turnbull[11] observed that the collateral circulation on the thorax and abdomen developed more frequently in the chronic than in the acute form. Occasionally the liver is found to be small when the syndrome is secondary to cirrhosis. Hydrothorax with ascites has been reported.[13, 24, 31] Albuminuria,[12] bilirubinuria,[12] bilirubinemia,[12] lowered plasma cholesterol,[38–41] absent cholesterol esters[24] and elevated blood urea nitrogen[24] are some of the abnormal laboratory findings infrequently found.

The syndrome must be differentiated from cirrhosis of the liver, acute hepatitis, thrombosis of the splenic veins, obstruction of the portal veins, constrictive pericarditis and acute pancreatitis. Abdominal pain — especially over the region of the liver — that sometimes radiates to the back and shoulders, enlargement of a smooth-edged liver and spleen, simultaneous rapid accumulation of ascites, resistance to diuretics, development of a collateral circulation and edema of the legs suggest Chiari's syndrome. The relatively short course of the disease, in addition to the absence of a nodular liver, jaundice, macrocytic anemia and spider angiomas, and normal liver-function studies differentiate the syndrome from portal cirrhosis. Peritoneoscopy also distinguishes the congested liver of Chiari's syndrome from the characteristic appearance in cirrhosis. Acute hepatitis is differentiated by the presence of jaundice, which is invariably absent in Chiari's syndrome, without rapidly accumulating ascites and peripheral edema, which are prominent in the cirrhosis.

Splenic-vein thrombosis is manifested by pain in the left upper quadrant, without tender enlargement

of the liver, ascites or peripheral edema. Obstruction of the portal vein is difficult to differentiate, except that there is rapid enlargement of the liver and formation of ascites with a caput medusae and dilatation of the veins of the abdominal wall. Jaundice, edema and anasarca are rare, and the condition is relatively benign, death being due to hemorrhage or intestinal infarction. Liver enlargement, jaundice and ascites are more marked in hepatic-vein than in portal-vein obstruction. In addition, there are usually leukopenia and anemia in Banti's syndrome.

Constrictive pericarditis is differentiated by a small heart, small pulse pressure, increased venous pressure in the upper as well as the lower extremities, paradoxic pulse, recurring ascites and edema of the lower extremities. Fluoroscopic, kymographic and electrocardiographic studies of the heart help to establish the diagnosis.

A primary tumor of the inferior vena cava may simulate the chronic form of Chiari's syndrome. These two conditions can sometimes be distinguished by the fact that the collateral circulation tends to flow caudad in hepatic vein obstruction and cephalad in inferior vena caval obstruction.

Acute pancreatitis is differentiated by the elevation of the serum amylase and lipase, and absence of a rapidly enlarging liver and symptoms of hepatic obstruction. In addition the shock in pancreatitis is usually out of proportion to the abdominal findings.

The onset of symptoms in the acute form of Chiari's syndrome has been mistakenly interpreted as indicating a surgical emergency of the abdomen.[7]

The pathologic changes in the liver in the syndrome depend on whether the hepatic thrombosis is acute or chronic. In the acute variety the liver appears enlarged, smooth, purplish and highly congested. Wedge-shaped areas are seen if there is occlusion of single branches. The changes microscopically resemble an infarct of Zahn. The central veins are distended or thrombosed, the sinusoids are packed with erythrocytes, and a few inflammatory cells are observed. The central portion of the liver lobule is congested with hemorrhage. Later degeneration and necrosis of the liver cells in this area are seen. If the patient recovers, pseudocirrhosis supervenes. The liver is nutmeg in appearance, nodular and granular, with regeneration of cells and connective-tissue hyperplasia as parenchymal replacement. All degrees of congestion, central necrosis, atrophy and fibrosis are seen, with different stages in various parts of the liver. Compensatory hypertrophy of the uninvolved liver cells occurs. The changes in the chronic form resemble those of cardiac cirrhosis. Such changes have been produced experimentally in animals.[42–47] Thrombosis of the hepatic veins produces portal hypertension and its resultant sequelae. Cirrhosis and primary carcinoma have been found superimposed in Chiari's syndrome in a significant number of cases. The relation is not understood, but it is suggestive that the presence of Chiari's syndrome predisposes to these lesions.

There are no known methods of treatment. Recovery or death depends on the rapidity of the obstruction of the hepatic venous drainage, the extent of the occlusion and the time required for canalization and the development of adequate circulation. Omentopexy resulted in death shortly after operation in several reported cases. Other operations to improve the circulation also terminated fatally.

Summary

A case of Chiari's syndrome due to an endophlebitis of the hepatic veins complicating peripheral and inferior vena caval thrombophlebitis is reported. The diagnosis was made during life and confirmed at autopsy. The literature is reviewed, and the differential diagnosis of this syndrome is presented.

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References

1. Budd, G. *Diseases of the Liver.* Third edition. 392 pp. Philadelphia: Lea and Blanchard, 1857. P. 195.
2. Chiari, H. Über die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache. *Beitr. z. path. Anat. u. z. allg. Path.* **26**:1-18, 1899.
3. Armstrong, C. D., and Carnes, W. H. Obstruction of hepatic veins (Chiari's disease): report of five cases. *Am. J. M. Sc.* **208**:470-478, 1944.
4. Kelsey, M. P., and Comfort, M. W. Occlusion of hepatic veins: review of twenty cases. *Arch. Int. Med.* **75**:175-183, 1945.
5. Kahn, S., and Spring, M. Thrombosis of hepatic veins — Chiari's syndrome: report of case with biopsy and venous pressure determination. *Ann. Int. Med.* **14**:1075-1083, 1940.
6. Hess, A. F. Fatal obliterating endophlebitis of hepatic veins. *Am. J. M. Sc.* **130**:986-1001, 1905.
7. Dickinson, A. M. Acute complete obstruction of hepatic veins: report of case simulating acute abdomen. *Surgery* **9**:567-570, 1941.
8. Satke, O. Endophlebitis obliterans hepatica. *Deutsches Arch. f. klin. Med.* **165**:330-353, 1929.
9. Berk, L. Über Thrombose der Lebervenen nach umschriebener Thrombose im hepatischen Stück der unteren Hohlvene. *Beitr. z. path. d. nat. u. z. allg. Path.* **909**:509-512, 1932.
10. Rigdon, R. H. On relation between thrombophlebitis of inferior vena cava and occlusion of hepatic veins (endophlebitis hepatica obliterans). *Bull. Johns Hopkins Hosp.* **53**:162-171, 1933.
11. Thompson, T., and Turnbull, H. M. Primary occlusion of ostia of hepatic veins. *Quart. J. Med.* **5**:277-296, 1912.
12. Baehr, G., and Klemperer, P. Thrombosis of portal and of hepatic veins. *M. Clin. North America* **14**:391-410, 1930.
13. Hoover, C. F. Obstruction of hepatic veins. *J. A. M. A.* **74**:1753-1759, 1920.
14. Jacobson, V. C., and Goodpasture, E. W. Occlusion of entire inferior vena cava by hypernephroma, with thrombosis of hepatic vein and its branches. *Arch. Int. Med.* **22**:86-95, 1918.
15. Kretz, R. Pathologie der Leber. *Ergebn. d. allg. Path. u. path. Anat.* **82**:473-537, 1902.
16. Rosenblatt, O. G. Über einen Fall von abnormen Verlauf der Lebervenen in Verbindung mit Cirrhose und Carcinom der Leber und consecutiver carcinomatöser Infiltration des Peritoneums. *Jahresb. ü. d. Leistung. d. ges. Med.* **1**:226, 1867.
17. Moore, F. C. Primary obliterative inflammation of main trunks of hepatic veins. *M. Chron.* **3**:240-251, 1902.
18. Hutchinson, R., and Simpson, S. L. Occlusion of hepatic veins with cirrhosis of liver. *Arch. Dis. Child.* **5**:167-186, 1930.
19. Gee, S. J. Complete obliteration of mouths of hepatic veins. *St. Barth. Hosp. Rep.* **7**:144-146, 1871.
20. Rolleston, H. D., and McNee, J. W. *Diseases of the Liver, Gallbladder, and Bile Ducts.* Third edition. 884 pp. London: The Macmillan Company, 1929.
21. Eppinger, H. *Die Leberkrankheiten: Allgemeine und spezielle Pathologie und Therapie der Leber.* 801 pp. Berlin: Julius Springer, 1937. P. 469.
22. Churton, T. Case of cirrhosis of liver, apparently due to congenital syphilis, with thrombosis of hepatic veins. *Tr. Path. Soc. London* **50**:145, 1899.
23. Nishikawa, Y. Über die Obliteration der Stammlebervenen und des heparen Hohlvenenabschnittes (Thrombophlebitis obliterans venae hepaticae et venae cavae inferioris). *Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo* **20**:151-305, 1918-1919.
24. Altschule, M. D., and White, G. Chiari's syndrome in patient with polycythemia vera: report of case. *New Eng. J. Med.* **220**:1030-1033, 1939.

25. Schüppel, O. Die Krankheiten der Venae hepaticae. In *Die Krankheiten der Gallenwege und der Pfortader.* Vol. 8. Part 2. 374 pp. *Handbuch der speciellen Pathologie und Therapie.* Edited by H. von Ziemssen. Leipzig: F. C. W. Vogel, 1880. Pp. 323-325.
26. Hallock, P., Watson, C. J., and Berman, L. Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease. *Arch. Int. Med.* **66**:50-61, 1940.
27. Savin, L. H. Clinical and post-mortem notes on case of "Budd's" (or Chiari's) disease, in which thrombosis of hepatic veins and of inferior vena cava was preceded, perhaps fortuitously, by exudative retinitis, iridocyclitis, and secondary glaucoma. *Tr. Ophth. Soc. U. Kingdom* **54**:326-337, 1934.
28. Sohval, A. R. Hepatic complications in polycythemia vera, with particular reference to thrombosis of hepatic and portal veins and hepatic cirrhosis. *Arch. Int. Med.* **62**:925-945, 1938.
29. Norman, I. L., and Allen, E. V. Vascular complications of polycythemia. *Am. Heart J.* **13**:257-274, 1937.
30. Cole, N. B. Comments on case of polycythemia rubra vera with autopsy. *M. Clin. North America* **16**:1255-1265, 1933.
31. McAlpin, K. R., and Smith, K. E. Polycythemia vera: report of fourteen cases treated with acetylphenylhydrazine. *New York State J. Med.* **38**:101-109, 1938.
32. Oppenheimer, B. S. Vascular occlusion in polycythemia vera. *Tr. A. Am. Physicians* **44**:338-344, 1929.
33. Ulhorn, E. Über Polycythämie mit Lebercirrhose. *Klin. Wchnschr.* **11**:2037, 1932.
34. Newman, C. Discussion of East.[36]
35. Lüdeke, H. Thrombophilie und Polycythämie. *Virchows Arch. f. path. Anat.* **293**:218-252, 1934.
36. East, T. Chiari's disease, with hypertrophic osteoarthropathy and familial lipomatosis. *Proc. Roy Soc. Med.* **26**:272, 1933.
37. Wilensky, A. O. Occurrence, distribution and pathogenesis of so-called liver death and/or hepatorenal syndrome. *Arch. Surg.* **38**: 625-691, 1939.
38. Adler, A., and Lemmel, H. Zur feineren Diagnostik der Leberkrankheiten. I. Cholesterin und Cholesterin-Ester im Blute Leberkranker. *Deutsches Arch. f. klin. Med.* **158**:173-213, 1928.
39. Feigl, J. Neue Untersuchungen über akute gelbe Leberatrophie. III. Fette und Lipoide des Blutes. *Biochem. Zschr.* **86**:1-47, 1918.
40. Epstein, E. Z. Cholesterol partition of blood plasma in parenchymatous diseases of liver. *Arch. Int. Med.* **47**:82-93, 1931.
41. Thannhauser, S. J., and Schaber, H. Über die Beziehungen des gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion. *Klin. Wchnschr.* **5**:252, 1926.
42. Simonds, J. P., and Brandes, W. W. Effect of obstruction of hepatic veins on systemic circulation. *Am. J. Physiol.* **72**:320-323, 1925.
43. *Idem.* Anaphylactic shock and mechanical obstruction of hepatic veins in dog. *J. Immunol.* **13**:1-10, 1927.
44. Simonds, J. P., and Callaway, J. W. Anatomical changes in livers of dogs following mechanical constriction of hepatic veins. *Am. J. Path.* **8**:159-166, 1932.
45. Simonds, J. P., and Jergesen, F. H. Late changes in liver induced by mechanical obstruction of hepatic veins. *Arch. Path.* **20**:571-581, 1935.
46. Bolton, C. Pathological changes in liver resulting from passive venous congestion experimentally produced. *J. Path. & Bact.* **19**:258-264, 1914.
47. Bolton, C., and Barnard, W. G. Pathological occurrences in liver in experimental venous stagnation. *J. Path. & Bact.* **34**:701-709, 1931.

RECURRENT SPONTANEOUS EMPHYSEMA OF THE MEDIASTINUM WITH CONCOMITANT PNEUMOTHORAX*

Report of a Case

J. D. SCHENDSTOK, M.D.†

ARUBA, CURACAO

EMPHYSEMA of the mediastinum has several times been reported in the older literature as a finding in patients with chest injuries or at autopsy. Its occurrence, however, as a disease entity with characteristic clinical symptoms and possible spontaneous onset has been shown only recently by several authors, especially Hamman[1] in 1934. Since that time the publication of a number of clinical reports gives the impression that the condition is not extremely rare.[2-4] A feature of clinical importance is the resemblance of some of the symptoms to those of coronary disease or myocardial infarction. The last fact may at the same time explain why the condition was apparently not recognized more frequently in the past.

The following case report serves as an illustration.

A 37-year-old American engineer was seen on December 22, 1942. The previous history was irrelevant except for three episodes of pain in the chest quoted from old records of the hospital, which are not discussed in detail since there was no definite proof that they were of the same nature as the symptoms described below.

On December 21 the patient had a tight feeling in the lower chest all day, which radiated to the left side of his neck. That evening, while he was sitting quietly in a chair, a rhythmic noise, apparently originating in the chest, struck his ear. The character of the noise was comparable to that of "water dropping on a shelf." The noise was loud enough to be noticed by his wife and by a visitor. One of the physicians of the hospital staff who was called stated that he could hear the sounds at 5 or 6 feet away from the patient's chest.

The patient was sent to the hospital the next morning for examination. He was still complaining about a tight feeling in the heart area but was not in acute distress. The pulse was 80 and slightly irregular and the respirations were normal, without dyspnea or cyanosis; the temperature was normal, and the blood pressure 100/70. Percussion of the heart and lungs revealed no abnormality except for an unusual amount of tympany over the heart area. There was a duplication of the 1st sound over all ostia but not with every heart beat. At that time no sounds could be heard except by stethoscope. A few extrasystoles were noted. No abdominal abnormality was observed, and the area of liver dullness was normal. The blood sedimentation rate (Westergren) was 8 mm. in 60 minutes, and the white-cell count was normal.

Roentgenologic examination following ingestion of barium suspension in Trendelenburg's and other positions failed to show either a diverticulum of the esophagus or a hernia of abdominal viscera through the esophageal hiatus or other sections of the diaphragm. The patient's complaints subsided in a short time.

He experienced no similar difficulties until May 31, 1943. That night, without any known cause, he again experienced a dull pain in the cardiac and left infraclavicular areas, and he and his wife noticed rhythmic sounds audible at a distance from his chest. He was seen as an ambulatory patient several times, but was finally hospitalized on June 7 because he did not improve.

When examined on June 1 the patient was not in acute distress, but the pain was still present and was worse when he walked. He was not shortwinded. Physical findings were reported normal, except for an increase of voice and breath sounds on the left side.

On June 2 it was found that the 1st heart sound was preceded by a fine clicking sound "like rales"; the 2nd sound was loud.

On June 5 the patient reported that he had heard the sounds in the chest again, especially associated with exercise, bending forward or getting up after lying down.

No new physical abnormalities developed during the 1st week after hospitalization. On June 1 examination of the blood showed a red-cell count of 4,020,000, with a hemoglobin of 84 per cent, and a white-cell count of 7550, with

*From the Hospital of the Lago Oil and Transport Company, Limited.
†Physician, Lago Oil and Transport Company, Limited.

1 per cent band and 73 per cent segmented neutrophils, 24 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 15 mm. in 60 minutes; the fasting blood sugar was 97 mg., and the nonprotein nitrogen 27 mg. per 100 cc. By June 7, the white-cell count had increased to 12,100, with 7 per cent band and 73 per cent segmented neutrophils and 20 per cent lymphocytes. The sedimentation rate was 15 mm. in 60 minutes. Routine stool and urine examination were negative. On June 10, the white-cell count was 11,400 with 76 per cent segmented neutrophils, 21 per cent lymphocytes, and 3 per cent eosinophils.

By June 13 the patient was feeling better. He could still hear the sounds when lying on his left side supporting himself on his arm and fixing his chest in a certain phase between inspiration and expiration. With the stethoscope a peculiar knocking sound could be heard that was not rhythmic but was apparently synchronous with some of the heartbeats although skipping others.

Several x-ray films of the lungs were taken during this period of observation. An anteroposterior film taken on June 1 showed a few areas of calcification about the left hilus and in the right lower lobe, and a scar in the left apex. No evidence of air in the mediastinum could be demonstrated. Films of the chest taken on June 2 in the right oblique position again showed no air in the mediastinum but revealed a small, marginal left-sided pneumothorax.

The patient was discharged from the hospital on June 20, feeling completely normal. X-ray films of the chest in the anteroposterior and right oblique positions taken on January 19, 1945, for the purpose of follow-up failed to show any recent disease.

Discussion

A comparison of the symptoms in the case presented above with those of several cases reported in the literature appears to justify the diagnosis of spontaneous mediastinal emphysema. A summary of the symptomatology in such cases follows.

Pain, which is a predominant feature, may be severe, moderate or, occasionally, entirely absent. In one of the few cases without pain a nocturnal coughing spell was the initial symptom.[5] The pain is usually located over the precordium, less frequently laterally in the left chest and seldom in the right chest. Radiation seems to occur more frequently to the back or neck than to the left arm.[3] The pain is often influenced by the position of the patient, increasing while he is lying on the left side.

True shock, dyspnea and cyanosis are not characteristic symptoms of this condition,[3] although Miller[6] reports dyspnea in his 4 cases. Marked changes of pulse rate and blood pressure are unusual. A slight elevation of the temperature is infrequently reported.

Inspection occasionally shows a decrease of expansion of the left side of the chest. A frequent and important sign is a tympanitic sound over the precordial area on percussion. A concomitant pneumothorax, often too small to cause any physical symptoms, need not be present to produce the condition.

Most characteristic are the auscultatory findings. The heartbeat may be audible without a stethoscope even at a considerable distance from the chest. This is due to the fact that the heart beats against air in the anterior mediastinum.[7]

With the stethoscope the sounds may be of a crunching, bubbling character, — like the noise caused by the crumpling of cellophane, — "boiler-like" or occasionally grating. They are usually systolic. The intensity of the sounds, like the pain, often increases when the patient turns on his left side.

Associated subcutaneous emphysema is an valuable aid in the diagnosis. It may be located in the neck or in the wall of the chest. The frequent concomitant pneumothorax is another way of escape of the air from the mediastinum.

Slight leukocytosis has occasionally been described.

Roentgenologically the air may be demonstrated in the mediastinum, often better in the oblique than in the anteroposterior view. The finding of a pneumothorax is easier and more frequently described than the demonstration of the air in the mediastinum itself. In view of the mechanism of development of this kind of pneumothorax it is likely that a late stage is represented, and that in the case reported above and similar cases the air had already moved from the mediastinum into the pleural cavity at the time of x-ray examination.

The prognosis in adults is apparently good. In the reports cited all patients recovered.

Most authors believe that spontaneous mediastinal emphysema is usually preceded by interstitial emphysema of the lungs. This condition is probably exceedingly frequent.

Small amounts of air in the pulmonary interstitium are probably resorbed. McGuire and Bean[8] make the following statement:

> If a large amount of air escapes it may travel along the interstitial bands toward the hilum and enter the mediastinum. A second, and perhaps commoner pathway for the air to follow is to pass outward directly to the pleura along interstitial bands where it causes the formation of a bleb which may rupture and produce an ordinary pneumothorax. The air may go in both directions, producing both results.

Macklin[9] inflated the bronchial tree of animals in experimental studies until the alveoli ruptured, and noticed that the air was usually transported to the hilus along the perivascular sheaths. Further inflation caused the air to collect in the mediastinum. Finally, the mediastinal wall ruptured and the air escaped into the pleural cavity.

A concomitant pneumothorax occurs frequently in cases of mediastinal emphysema. Macklin believes that it develops in the same way as in his experimental animals. It is remarkable that, so far, such pneumothorax has always been found on the left side.

Summary

A case of recurrent spontaneous emphysema of the mediastinum, with concomitant pneumothorax, is reported, and the mechanism responsible for this condition is discussed.

References

1. Hamman, L. Remarks on diagnosis of coronary occlusion. *Ann. Int. Med.* **8**:417-431, 1934.
2. *Idem.* Spontaneous interstitial emphysema of lungs. *Tr. A. Am. Physicians* **52**:311-319, 1937.
3. *Idem.* Spontaneous mediastinal emphysema. *Bull. Johns Hopkins Hosp.* **64**:1-21, 1939.
4. *Idem.* Note on mechanism of spontaneous pneumothorax. *Ann. Int. Med.* **13**:923-927, 1939.
5. Caldwell, H. W. Spontaneous mediastinal emphysema. *J. A. M. A.* **116**:301, 1941.
6. Miller, H. Spontaneous mediastinal emphysema with pneumothorax simulating organic heart disease. *Am. J. M. Sc.* **209**:211-220, 1945.
7. Greene, J. A. Unusual sounds emanating from chest: cause and diagnostic significance of bubbling, clicking, crunching, knocking and tapping sounds, with report of two cases of interstitial emphysema of lung and mediastinum. *Arch. Int. Med.* **71**:410-414, 1943.
8. McGuire, J., and Bean, W. B. Spontaneous interstitial emphysema of lungs. *Am. J. M. Sc.* **197**:502-509, 1939.
9. Macklin, C. C. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implications. *Arch. Int. Med.* **64**:913-926, 1939.

UNILATERAL TREMOR OF THE LOWER EXTREMITY*

Its Association with Internal Derangement of the Ipsilateral Knee

LIEUTENANT COLONEL CHARLES J. SUTRO, M.C., A.U.S.

ON orthopedic examination of 500 soldiers with recent or long-standing post-traumatic lesions of the knee, the existence of a bizarre type of intentional tremor involving the ipsilateral lower extremity was noted in 8. Most of these 500 soldiers had experienced pain in their knees in civilian life. Each of the 8 soldiers in question complained of recurrent swelling and pain of a single knee and weakness of the ipsilateral leg. Three of the 8 were not able actively to extend the affected leg to 180°, and this was first noted from three to ten years prior to entrance into the armed forces. The tremor was encountered when the involved leg was held in an actively extended attitude of 150° or more. Of further interest was the observation that the existence of this tremor was of more value than atrophy of the thigh in predicting the status of work efficiency of the quadriceps apparatus. Furthermore, the finding of a tremor of a single lower extremity as noted in this study suggested the possibility of a psychosomatic disturbance. On this basis, the test for the tremor provided a ready means to detect psychosomatic disorders in patients with derangement of the knees. It was believed that patients with such tremors were not suitable for elective orthopedic procedures without adequate psychiatric study. An investigation based on the examination of these 8 patients is presented.

Procedure

The patient was seated on the examining table or chair in a position to permit active excursion of the lower extremities. The involved leg was actively extended to its maximal degree, while the opposite leg was held in a relaxed attitude at approximately 90° of flexion. When the test gave a positive reaction, a tremor involving the entire affected extremity, with repeated short excursions of the leg in flexion and extension, was noted from thirty to sixty seconds after the leg was extended to its maximal degree. This tremor, which caused a vertical oscillation of the extremity from one hundred to five hundred times a minute, without any pattern or fixed rhythm, lasted uninterruptedly for ten minutes — the maximum period of observation. The tremor could be terminated quickly by actively or passively flexing the affected leg to an angle of approximately 90°. The height of the vertical oscillation as measured at the toes varied from 2.5 to 7.5 cm. The patients had no voluntary control over the rate or altitude of the tremor. Furthermore, the use of sedatives, such as phenobarbital and amytal in doses of 65 mg., produced no visible effect on the rapidity of the onset, rate or altitude of the oscillation of the leg. When the examiner percussed the flexed knee of the normal leg of the patient, a temporary increase in the rate and height of the tremor of the affected extended leg was noted. When both legs were simultaneously extended, the tremor was present only in the one with the involved knee (Fig. 1). Infrequently a very mild tremor of transitory nature was observed in the opposite uninvolved extended leg or upper extremities. In 4 of the 8 patients, hyperventilation became apparent four or five minutes after the onset of this test and was accompanied by severe pain in the affected limb. These tests for tremor were repeated each month during the period of two to fourteen months' observation.

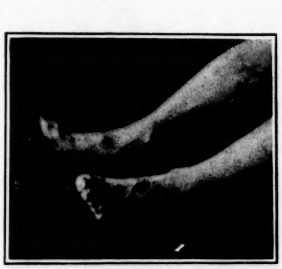

FIGURE 1. *Photograph of the Lower Extremities. Note that the right foot is out of focus because of the tremor.*

*From the Station Hospital, Fort Riley, Kansas.

TABLE 1. *Clinical Findings in 8 Patients with Tremor of the Lower Extremity Associated with Previous Injury to the Knee.*

Case No.	Age at Admission	Length of Service on Admission	Period after Initial Trauma	Local Symptoms Following Initial Trauma	Atrophy of Quadriceps Muscles	Movements at Knee	Psychiatric Diagnosis	X-Ray Examination of Knee	Operation	Diagnosis	Total Period of Observation and Follow-Up	Disposition of Patient
	yr.	mo.									mo.	
1	25	3	3 yr.	Swelling and pain	Mild	5° restriction to complete active and passive extension of leg	Anxiety neurosis	Negative	None	Flexion contracture (cause undetermined)	3	Separated from service
2	18	1	18 mo.	Swelling, pain and locking	Extreme	Free	Normal	Negative	None	Fissure of articular cartilage of patella	13	Retained in service
3*	20	20	2 mo.	Swelling, pain and locking	Extreme	Free	Anxiety neurosis	Negative	Arthrotomy (fissure of articular femoral cartilage)	Fissure of articular femoral cartilage	16	Separated from service
4	21	1	6 yr.	Swelling and pain	None	Free	Normal	Osteochondritis dissecans of femoral condyle	None	Osteochondritis dissecans of femoral condyle	2	Separated from service
5°	24	4	4 mo.	Swelling and pain	Extreme	Free	Mild anxiety neurosis	Negative	Arthrotomy (fissure of articular femoral cartilage)	Fissure of articular femoral cartilage	12	Retained in service
6	24	9	4 yr.	Swelling and pain	Mild	5° restriction to active extension of leg; passive extension free.	Anxiety neurosis	Negative	None	Fissure of articular cartilage of patella	12	Separated from service
7	26	12	4 yr.	Swelling and pain	Extreme	5° restriction to complete active and passive extension of leg	Anxiety neurosis	Negative	None	Flexion contracture (cause undetermined)	12	Separated from service
8	35	6	19 yr.	Swelling and pain	Mild	5° restriction to complete active and passive extension of leg	Anxiety neurosis	Negative	None	Flexion contracture (cause undetermined)	4	Separated from service

*Knee injury incurred in line of duty.

Clinical Findings

Table 1 summarizes the clinical findings.

Psychiatric examination revealed that 6 of the 8 patients exhibited general evidence of anxiety neurosis. Only 1, who had had symptoms for ten years, knew prior to these examinations that the involved extremity presented a tremor.

Two patients with service-incurred injuries to the articular cartilage of the femur developed a tremor of the affected limb after arthrotomy of the knee. They also showed definite physical findings frequently observed in states of anxiety. When 1 of these soldiers was placed in a branch of the service for which he expressed a specific preference, an excellent recovery was obtained. The tremor had completely disappeared within a year after the operation, although marked atrophy of the quadriceps muscles persisted. This soldier could fully extend the leg of the affected limb against a considerable amount of resistance to the extensor apparatus. The other soldier was treated in the reconditioning, orthopedic and psychiatric sections for a period of sixteen months without any amelioration in the status of the tremor of the limb. It was believed that the environment was a predisposing basis for many of his difficulties. He was, therefore, separated from the Army.

In the nonoperative group of 6, all but 1 of the soldiers were separated from the service. In spite of psychiatric, reconditioning and orthopedic treatment, no improvement was obtained either in the mental or in the physical reactions of these 5 soldiers. In the soldier in whom an excellent adjustment was made, re-examination a year later revealed an absence of the tremor of the affected leg, with a persistence of the atrophy of the quadriceps muscles. This soldier is performing regular duty in the armed forces.

Discussion

One gains the impression that the tremor demonstrated in these 8 cases was similar to that noted in hands affected with writer's cramps or fatigue neurosis. In parallel investigations, a similar tremor was temporarily produced in lower extremities that had recently been immobilized in plaster of Paris bandages for three or more months for treatment of a fractured leg. With exercises and training, the tremor disappeared rapidly in the patients who did not present any tendency toward an anxiety state. From the observations made in these studies, it was suspected that a psychosomatic disturbance had considerable influence on the production and extent of duration of this tremor. For that reason arthrotomy, when indicated, was postponed until a complete psychiatric study had been made. Most soldiers with derangement of the knees who had such tremors were separated from the service without surgical intervention, since it was almost impossible to obtain a complete mental and physical recovery in the military environment. A change to civilian life was therefore suggested as part of the preoperative and postoperative care of such patients.

Undoubtedly the same sequence of events occurs in persons whose knees are injured in industrial or other accidents, and the identical method of handling such cases appears indicated. The tremor must be differentiated from that caused by malingering, Parkinson's disease or Wilson's disease.[1–9]

Summary

In a group of 500 soldiers with lesions affecting the knee, in 8 there was a coarse tremor limited to the ipsilateral lower extremity that was brought out by active extension of the leg. Six of these patients so affected presented evidence of anxiety states. In 2 of the 8 soldiers the tremor developed after arthrotomy of the knee was performed. Only 1 of the 2 made a complete recovery after vocational readjustment. The other was separated from the service because of aggravation of the tremor. In the nonoperative group of 6, only 1 patient made a recovery after vocational readjustment. The other 5 were separated from the service because the environment was considered to have a decided influence on the persistence of the tremor and symptoms.

The finding of such a tremor in association with lesions of the knee suggests the existence of an anxiety neurosis. When noted, especially in connection with an industrial or other accident or in a member of the armed forces, arthrotomy of the knee should be postponed or avoided until complete psychiatric examination and treatment are pursued. Change in environment, such as separation from the service, is recommended as part of the treatment.

Examination to determine the presence or absence of such tremor is suggested as a routine measure in patients with derangement of the knee joint.

References

1. Jones, A. B., and Llewellyn, L. J. *Malingering or the Simulation of Disease*. 708 pp. Philadelphia: P. Blakiston's Son and Company, 1917.
2. Johnson, W. Hysterical tremor. *Brit. M. J.* **2**:627, 1918.
3. Church, A., and Peterson, F. *Nervous and Mental Diseases*. Ninth edition. 949 pp. Philadelphia: W. B. Saunders Company, 1919.
4. Ford, F. R. Clinical demonstration of several types of tremor with brief discussion of their significance. *Internat. Clin.* **1**:175-189, 1933.
5. Young, I. C. Study of tremor in normal subjects. *J. Exper. Psychol.* **16**:644-656, 1933.
6. Smith, L. A., and Eaton, L. M. Orthostatic tremor. *Proc. Staff Meet., Mayo Clin.* **17**:122-126, 1942.
7. *The Precentral Motor Cortex*. Edited by Paul C. Bucy. 605 pp. Urbana, Illinois: University of Illinois Press, 1944. Pp. 399-408.
8. Brazier, M. A. B. Tremors of combat neuroses: comparison with tremors of paralysis agitans, delirium tremens and psychoneuroses of civilian life: electromyographic studies. *Arch. Neurol. & Psychiat.* **54**:175-180, 1945.
9. Homburger, F., and Kozol, H. L. Hepatolenticular degeneration. *J. A. M. A.* **130**:6-14, 1946.

MEDICAL PROGRESS

PRESENT CONCEPTS OF BENIGN BREAST DISEASE*

IRA T. NATHANSON, M.D.†

BOSTON

ADVANCES in knowledge of factors concerned in mammary development and function have considerably changed concepts of breast disease in human patients. Through information resulting from systematic surveys, histories, examinations and experimental studies, a new approach to the problem has become available. Since it was demonstrated that hormones were involved in the physiologic response of the breast, it became obvious that they might be of major importance in the genesis of diseases of the mammary gland. Thus, a comprehension of the histology and physiology of the gland is essential to a better understanding of factors that are of possible significance in the initiation of benign and malignant breast lesions. Reviews of the endocrine physiology of the breast have appeared elsewhere,[1-3] so that the following discussion is limited to the more pertinent studies. It should be pointed out that much of the present knowledge of the breast is based on animal experimentation; such data are of extreme value, but as has previously been pointed out, caution in the interpretation as applied to human material is necessary.[4] It is the purpose of this paper to evaluate the available information and to indicate present trends of thought regarding breast disease in human beings.

PHYSIOLOGIC CHANGES

The mammary gland must be considered a part of the female reproductive system and, as such, subject to the same stimuli throughout life as the other organs of reproduction. Changes in the breast seem to be directly related to those occurring in the uterus during the various phases of pituitary and ovarian activity and during pregnancy. Using this concept as a basis, one may review with greater clarity the changes at various periods of life.

At Birth

Activity of the mammary ducts in newborn infants of both sexes is frequent. In addition, mammary enlargement (mastitis neonatorum) and secretion (witch's milk) may occur. These changes originate from endocrine stimuli of maternal origin, since cessation of function and regression of the active processes in the breast follow shortly after delivery.

At Puberty

After birth the breasts are inactive until the appearance of changes leading to puberty. In the female, development of the breast, which usually begins at about the tenth year, is associated with a definite increase in the activity of the gonads.[6] At first the changes are confined to the ducts and periductal connective tissue, but even before the menarche there is evidence of acinar and lobule formation. Changes may also be noted in the male breast between the ages of twelve and seventeen.[6] The histologic picture is similar to that observed at the onset of breast growth in the female. These changes usually subside spontaneously in contrast to those in the female, in which mammary development usually continues once the cyclic activity of the menses is established.

In Cyclic Women

There is convincing evidence that cyclic changes occur in the breast that can be correlated with a rise and fall in ovarian activity during the menstrual cycle.[7-13] Whether these changes are purely epithelial, vascular, secretory or combinations of these is a matter of dispute. Such divergencies of opinion are understandable when it is recognized that studies of whole sections of the breast showed that the degree of activity is not similar throughout.[14] This has been attributed to the lack of a uniform response to a given stimulus, that is tissue sensitivity and, as pointed out below, may be a determining factor in certain types of breast disease. Moreover, many of the studies were made on small areas of breast tissue removed coincidentally with localized pathologic processes and therefore should not be considered typical of the normal breast. Review of breast tissue removed from patients dying from various causes is subject to the criticism that the structures may have been altered as a result of the primary disease. Thus, it is apparent that no concrete concept of the changes can be complete until whole sections are made from many normal breasts throughout the menstrual cycle. This is a difficult task, but Foote and Stewart[15] have made an excellent attempt to study such changes from material obtained from apparently healthy women who died accidentally. They were able to predict, with a high percentage of success, the stage of the menstrual cycle from a study of the breast tissue. Since cyclic changes in the endometrium are well recognized and the stage of the menstrual cycle can be determined with con-

*From the Medical Laboratories of the Collis P. Huntington Memorial Hospital and the Tumor Clinic of the Massachusetts General Hospital, Boston, and the Pondville Hospital (Massachusetts Department of Public Health), Walpole, Massachusetts.

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†Associate in surgery, Harvard Medical School; assistant surgeon, Massachusetts General Hospital and Pondville Hospital.

siderable accuracy from the endometrial pattern, they utilized this technic as a control. They further found that the status of the breast — particularly of the lobule — in post-mortem material was vastly different from that in surgical specimens.

Complete development of the breast is manifested by the presence of certain static structures (ducts, lobules and acini). Variations of these structures may occur during the menstrual cycle as a result of rhythmic stimulation with the hormones. The breast is prepared each month for pregnancy, since it is subject to the same influence as the uterus.[3] Like the uterus it has both a proliferative phase induced by estrogens and a secretory phase effected by progestin and the anterior lobe of the pituitary gland. A process analogous to menstruation then occurs and is represented by an involutional change and absorption of the secretion if pregnancy does not ensue. It is only by accepting these possibilities that one may have a concise and logical explanation for the hormonal and nervous action on the breast with the resultant changes during catamenia, pregnancy, lactation and the pathologic states described below.

In Pregnancy and Lactation

Changes during pregnancy and lactation are well recognized and are certainly controlled to a large extent by hormonal secretion. The alterations in the breast in the first half of pregnancy are rapid growth of the lobules and epithelial proliferation; in the latter half the acinar epithelium enlarges and secretes and thus causes distention of the acini.[2] During pregnancy the placenta is probably the main source of stimulation, whereas during lactation the pituitary gland is the likeliest dominant activator of mammary function.

At the Climacteric

At the menopause, when ovarian stimuli recede to a low ebb, the mammary gland exhibits regressive changes. In some cases evidence of activity in the breast is apparent years after the cessation of the menses. Such activity may be caused by continued but lowered secretion of an activating hormone, possibly from the ovary. In other cases, particularly late in life, there may be an almost complete atrophy of the gland.

In summary, it may be stated that mammary development, growth and regressive changes depend on the rise and fall of hormonal stimuli principally from the gonads and the hypophysis. The exact mechanism by which the metamorphosis takes place is not fully understood. Present knowledge, however, allows at least a working hypothesis for the understanding of some of the diseases of the breast described below.

The Nervous System

Evidence exists that the nervous system is involved in some fashion in the physiologic responses of the breast. Suckling in the virgin rat resulted in mammary development, lactation and inhibition of the estrous cycle.[15] This presumably works reflexly by way of the hypophysis. In women, suckling certainly plays an important role in the maintenance of lactation. Moreover, numerous cases are cited of lactation and breast changes in children, the virgin female and even in the male after stimulation of the nipple alone.[14] Many lesions of the breast are associated with disease in the pelvis that affects the breast not only by disturbance of ovarian function but also by way of the pelvic sympathetic nerves.[11] It must be inferred therefore that the nervous system is important for the maintenance of mammary function, but probably in an indirect manner since the elaboration of hormones may be partially initiated by or dependent upon nervous stimuli.

Precocious Development (Infantile Hypertrophy)

Aside from the changes noted at birth there are numerous cases of premature mammary development in children. These are usually associated with demonstrable lesions, although in some cases the etiology is vague.

Lesions of the third ventricle. Tumors, defects and inflammatory lesions in the region of the third ventricle give rise to true pubertas praecox. The breast changes are merely part of the general picture of developmental and sexual advance. The most probable explanation for the effect is a stimulation of the hypophysis via the hypothalamus and infundibulum. The breasts exhibit ductal development but rarely lobule formation. Ovaries of these patients show marked follicle development and cyst formation, and in 1 case a true corpus luteum was reported suggesting stimulation by the hypophysis.[16] This activity in the ovary probably initiates the secretion of the hormones, which in turn causes growth of the secondary sex organs, including the breast. This thesis is confirmed by assays of the urine of these patients, which usually show increased levels of gonadotropic hormone, estrogens and 17-ketosteroids (androgens).[17]

Lesions of the adrenal cortex. In general, neoplasms or hyperplasias of the adrenal cortex in the female child produce masculinization, but there are cases in which the first signs are feminization.[18] Because the adrenal glands are a probable source of estrogens it is possible to explain the early mammary hypertrophy on this basis, especially since excretion studies reveal increased amounts of the hormone.[16] When masculinization and regression of the breast occur they are accompanied by a significant increase in the androgenic output, even though the estrogen levels usually remain elevated. Thus, it is reasonable to assume that this reversal is of androgenic origin and therefore that the androgens

are not responsible for the original breast hypertrophy.

Ovarian lesions. Among the associated exciting factors of premature mammary development are lesions such as the granulosa-cell tumor and teratoma of the ovary. These lesions, when active, are usually associated with generalized feminization, breast enlargement, uterine bleeding and cornification of the vaginal epithelium. This syndrome must be distinguished from true pubertas praecox. As in the other states, however, the breast changes are probably produced by estrogens elaborated by the tumors, since the cells involved presumably secrete the hormone. Assays of the urine in most cases reveal elevated excretion levels of estrogens, whereas the titers of the other hormones remain normal.[18]

Idiopathic breast development. In some children premature breast development occurs without known cause. The process may be transient or may persist. Other secondary sex changes are usually normal or only slightly advanced. Histologic examination reveals ductal development, but for the most part assays of the urine for hormones do not reveal any abnormalities. In the syndrome of osteitis fibrosa disseminata, breast enlargement is a part of the associated sexual precocity.[19]

Hormone-induced infantile hypertrophy. It has been the experience of many that administration of estrogenic hormone to the female child for gonorrheal vaginitis frequently results in mammary growth. There is no question that these changes are due to the hormone, since regression occurs rather rapidly after cessation of treatment.

In summary, the available evidence suggests that premature mammary development is due in large part to hormonal stimulation. Histologically the changes are confined for the most part to the duct system and periductal connective tissue. Thus, they correspond to a state produced by a known stimulus (estrogens) and in this sense represent a physiologic response to premature or excess secretion of the hormones, as a result of endocrine disturbances. Removal of such a stimulus is followed by a rapid regression to the normal state. Of significance is the fact that precocious development of the breast may be an indication of a pathologic state elsewhere, and as such may be a valuable aid in diagnosis.

Hypertrophy

Asymmetrical prepubertal hypertrophy. At about the age of ten, when normal breast development usually begins, there may be a rapid growth of one breast that is out of proportion to that of the other. This is often referred to as "early ripening" and is not true hypertrophy. Eventually the more slowly developing breast usually attains the size of the larger breast, and at the time of puberty both are of almost equal size and within normal limits. Since in most females the breasts are not identical in size, this seems to represent an exaggeration of a normal phenomenon. Histologically the changes are no different from those in the normal adolescent. Estrogen excretion is usually normal. The early inequality is explained by some investigators as an increased sensitivity of the involved organ to a normal physiologic stimulus.

Pubertal and postpubertal hypertrophy. Pubertal and postpubertal hypertrophic abnormalities may be classed as true hypertrophy. The process is either unilateral or bilateral and is easily distinguished from early ripening by the size of the breast. It may first manifest itself at puberty, although similar changes are associated with pregnancy and lactation. Histologically there is an increase in ductal growth, but connective-tissue increase is more striking. Lobular development is rare especially in the virginal type. Estrogen assays are usually normal but may show elevated levels of the hormone. Again, as in early ripening, the changes may be due to an excessive stimulation or to increased sensitivity of the breast involved.

Fibroadenoma

Fibroadenomas of the breast are the most frequent tumors in young women, the majority appearing between the second and third decades. The lesions are generally slowly growing and although not noticed may arise in the early years after the menarche, when atypical menstrual activity is not unusual; they resemble the changes seen in early ripening and hypertrophy. They are rare before puberty and after the menopause, except possibly in the presence of a granulosa-cell tumor of the ovary. It has been suggested that the greatest incidence of the tumor is in women of a definite constitutional type — nulliparous women with a relative underdevelopment of the pelvic organs and breast.[20] Fibroadenomas are also found, however, in association with hypertrophy of the breast in a small percentage of cases. Changes have been observed in the size and histologic appearance of these tumors during the menstrual cycle,[10] pregnancy and lactation.[21, 22]

Fibroadenomas are distinctly different from other lesions of the breast, in that they may respond to a stimulus in the same fashion as normal breast tissue. It has therefore been suggested that they are not true tumors but merely a localized response to a normal stimulus as a result of a specific tissue sensitivity; such a response is akin to the grosser manifestations of early ripening and asymmetrical hypertrophy. This thesis is enhanced by the fact that the lesions may be multiple and may continue to appear as mammary development progresses. In addition, areas resembling fibroadenomas may be found in a breast without actual formation of a mass. Observation suggests that these lesions are of hormonal origin. It is possible that they arise as a result of abnormal or excessive stimulation, since they usually

occur when the metabolism and secretion of the sex hormones are at their height and may be abnormal as well. It is difficult to explain why circulating hormones do not affect the breast tissue in a uniform manner, but as stated above, present evidence suggests that such lack of uniformity exists and probably depends on individual susceptibility.[10, 23]

Chronic Cystic Mastitis

As pointed out frequently in the last few years, both clinicians and pathologists often use this terminology as a catchall for a variety of benign lesions without tumor formation. It is now recognized that some of the lesions included under the diagnosis of chronic cystic mastitis can be distinguished as definite entities and should be so designated. I am fully in accord with this point of view and plead that the term chronic cystic mastitis be discarded. It is essential that a working classification based on clinical and microscopic evidence be established for an investigation of possible causative factors and the natural history of any specific lesion. A number of writers have attempted to establish such a classification, but because of variations in interpretation and nomenclature, confusion exists even among those who have made special efforts to study the problem, owing partly to the difficulty in observing a process as it develops and partly to the variety of changes that coexist in the same breast. At any rate, the situation is being clarified, and it is likely that agreement among the various workers will be forthcoming as more material is studied and correlated. The importance of unanimity of opinion lies in the fact that some lesions included in the diagnosis of chronic cystic mastitis may lead to cancer, whereas others may be of no significance. Discussions dealing with this subject should be reviewed and evaluated by the interested reader[3, 13, 14, 24–30] It is not within the realm of this review to attempt a conciliation of apparently contradictory viewpoints. Nevertheless a description of clinical syndromes frequently seen is indicated, to stimulate further investigation and clarification.

A syndrome in which the earlier signs are characterized by premenstrual swelling and pain associated with tenderness on palpation seems to be a distinct entity. The relief following the onset of the menses is dramatic. It is recognized that similar symptoms may be present in apparently normal women and, as has been stressed, may be an integral part of the normal breast cycle in preparation for pregnancy. The patients seen by the physician, however, usually have an aberration of an apparently normal process. The early physical signs are usually minimal and, besides slight premenstrual swelling and venous engorgement, may reveal only a slight thickening in the upper outer quadrant. Histologically there may be only a slight increase in the periacinar connective tissue and edema. As the process continues the symptoms and signs become more prominent. There may be only an accentuation of nodularity in the upper outer quadrant, but usually the process is more extensive. There may be an increase in the density of the breast, which is well differentiated from the overlying skin, the subcutaneous tissue and the underlying structures. In the advanced stages the entire breast resembles a saucer or disk, and a definite edge can be palpated. The gland may be finely granular or nodular and in the premenstruum exhibits marked swelling and venous dilatation that may account for the cyclic pain. On microscopic examination there is usually a marked increase in the connective stroma, with loss of or defective lobule formation. Frequently, in addition, there is proliferation of the acini, although the epithelium itself is not hyperplastic. Many variations of the process are seen. These lesions usually occur in the second and third decades of life in women who have not been pregnant. The process resembles both clinically and histologically the localized fibroadenoma. Menstrual cycles may be of shorter intervals than usual, accompanied by a scant flow of short duration. The incidence of sterility is high, and in women who have borne children the lesion is sometimes seen after a long period of infertility. Terms suggested for such processes are "adenofibrosis,"[24] "lobule alteration"[13] and "fibroadenomatosis."[25] The secretions of the ovaries seem to be a prerequisite for the production of this syndrome, although they may not be the exciting factors. Nervous stimuli, vascular reaction and the mechanisms of hormonal secretion are closely interwoven, so that all three factors may be involved in the process, particularly regarding the edema and congestion. Excretion studies are slightly suggestive of a hormonal imbalance. The possible role of unopposed or atypical stimulation by the hormones also remains to be clarified. Slight abnormalities in the menstrual cycle and associated pelvic disease suggest a hormonal etiology. It can be concluded that, as in fibroadenoma, the hormones are involved but that other factors are necessary for the production of the syndrome.

Another lesion is characterized by discharge from the nipple. The process is sometimes associated with swelling and cyclic or acyclic pain. The discharge may abate at the menses, but generally persists throughout the cycle. It may be serous or may resemble colostrum and show varying degrees of viscosity. It is to be distinguished from the serosanguinous or sanguinous discharge frequently associated with duct papillomas, marked epithelial hyperplasias and carcinoma. Examination usually reveals dilatation of the ducts that is sometimes segmental and simulates cysts, especially near the areola. The dilated ducts can usually be palpated as cordlike structures radiating from the nipple. Slight nodularity may be found elsewhere in the breast. The nipples are frequently crusted, the mammary tissue itself is ill defined, and the breast

is lax. If secretion is not obvious, removal of the crust, with gentle pressure on the breast, usually results in the escape of fluid from the nipple. On gross and microscopic examination the ducts are dilated and contain secretion, desquamated cells and debris. Cheesy, inspissated material and segmental dilatations, which appear cystic, are often seen. Hyperplasia of the duct and acinar epithelium may be superimposed. A sequel of duct stasis and dilatation may be erosion of the epithelial lining.[23] If the surrounding stroma is fatty, a reaction as manifested by fat necrosis may be seen. These lesions occur most frequently during the third and fourth decades of life. Many cases appear at onset of the menopause. Remission of symptoms and signs is frequent after castration or when the menopause is complete. The menstrual cycles may be normal, but prolongation of the interval is not unusual. In contrast to the findings in adenofibrosis, the endometrium is often atypical. Absence of the secretory phase is a frequent finding, although hyperplasia is relatively rare.[3] Many women with this disease have borne children. Lactation may be normal, but faulty lactation or premature weaning precedes the onset of the disease in many cases. Pelvic disease occurs fairly often in this group. Ovarian cysts predominate over other abnormalities. This type of lesion has been referred to as "nonpuerperal secretion,"[23, 24] "periductal mastitis," "microcystic fibroadenomatosis,"[25] and "benign parenchymatous hyperplasia."[27] Nonpuerperal secretion and associated processes, which seem to be due to endocrine dysfunction and are akin to lactation, are frequently allied with abnormalities of the process, occurring as a sequel to it as a result of incomplete involution or from the continuation of the lactation. This syndrome is probably due to an ovarian dysfunction in which the normal cyclic secretion of hormones is absent. Such a condition is suggestive of an anovular cycle, a state that often occurs in the premenopausal period when these breast lesions may make their appearance.

Unfortunately, many of the lesions seen by the clinician are not so clear cut as those described above. There may be combinations of adenofibrosis and nonpuerperal secretion. Other cases show, in addition, cyst and papillomatous formation,[24] which may be superimposed on the two basic processes. Such a phenomenon occurs when the less complicated lesions are of long standing and are subjected to continuous or new stimulation. This group of mixed lesions leads to great confusion in diagnosis and interpretation of causative factors. At present, because of an incomplete understanding of these types, it is difficult to evaluate possible exciting factors. Lesions resembling the various types have been produced in animals by various hormones, particularly the estrogens. At any rate, it is possible that factors concerned in the production of the more clear-cut lesions are involved in this heterogeneous group as well.

(To be concluded)

References

1. Nelson, W. O. Endocrine control of mammary gland. *Physiol. Rev.* **16**:488-526, 1936.
2. Turner, C. W. The mammary glands. In: *Sex and Internal Secretions: A survey of recent research.* Second edition. 1346 pp. Edited by E. Allen, C. H. Danforth and E. A. Doisy. Baltimore: Williams & Wilkins Company, 1939. Pp. 740-803.
3. Nathanson, I. T. Relationship of hormones to diseases of breast. *Surgery* **16**:108-140, 1944.
4. Nathanson, I. T. Endocrine aspects of cancer. *New Eng. J. Med.* **231**:764-770, and 795-802, 1944.
5. Nathanson, I. T., Towne, L. E., and Aub, J. C. Normal excretion of sex hormones in childhood. *Endocrinology* **28**:851-865, 1941.
6. Jung, F. T., and Shafton, A. L. Mastitis, mazoplasia and gynecomastia in normal adolescent males. *Illinois M. J.* **73**:115-123, 1938.
7. Rosenburg, A. Über menstruelle, durch das Corpus luteum bedingte Mammaveränderungen. *Frankfurt. Ztschr. f. Path.* **27**:466-506, 1922.
8. Dieckmann, H. Über die Histologie der Brustdrüse bei gestörtem und ungestörtem Menstruationsablauf. *Virchows Arch. f. path. Anat.* **256**:321-356, 1925.
9. Polano, O. Untersuchungen über die zyklischen Veränderungen der weiblichen Brust während der Geschlechtsreife. *Ztschr. f. Geburtsh. u. Gynäk.* **87**:363-373, 1924.
10. Ingleby, H. Relation of fibro-adenoma and chronic mastitis to sexual cycle changes in breast. *Arch. Path.* **14**:21-41, 1932.
11. Taylor, H. C., Jr. Relation of chronic mastitis to certain hormones of ovary and pituitary and to coincident gynecological lesions: theoretical considerations and histological studies. *Surg., Gynec. & Obst.* **62**:129-148, and 562-584, 1936.
12. Geschickter, C. *Diseases of the Breast: Diagnosis, pathology, treatment.* 829 pp. Philadelphia: J. B. Lippincott Company, 1943.
13. Foote, F. W., and Stewart, F. W. Comparative studies of cancerous versus noncancerous breasts. *Ann. Surg.* **121**:6-53 and 197-222, 1945.
14. Cheatle, G. L., and Cutler, M. *Tumours of the Breast: Their pathology, symptoms, diagnosis and treatment.* 596 pp. London: Edward Arnold and Company, 1931.
15. Selye, H., Collip, J. B., and Thomson, D. L. Nervous and hormonal factors in lactation. *Endocrinology* **18**:237-248, 1934.
16. Nathanson, I. T., Aub, J. C., Farber, S., and Cutler, C. H. Generalized effects of hyperfunctioning endocrine tumors in childhood. Presented at Third International Cancer Congress, Atlantic City, 1939.
17. Nathanson, I. T., and Aub, J. C. Excretion of sex hormones in abnormalities of puberty. *J. Clin. Endocrinol.* **3**:321-330, 1943.
18. Friedgood, H. B., and Gargill, S. L. Biochemical and clinical studies of virilism before and after removal of adrenal cortical tumors. *J. Clin. Investigation* **17**:504, 1938.
19. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P. H. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of 5 cases. *New Eng. J. Med.* **216**:727-746, 1937.
20. Taylor, H. C., Jr. Evidence for endocrine factor in etiology of mammary tumors. *Am. J. Cancer* **27**:525-541, 1936.
21. Kilgore, A. R. Tumors and tumor-like lesions of breast in association with pregnancy and lactation. *Arch. Surg.* **18**:2079-2098, 1929.
22. Geschickter, C. F., and Lewis, D. Pregnancy and lactation changes in fibroadenoma of breast. *Brit. M. J.* **1**:499-504, 1938.
23. Geschickter, C. F. Breast pathology in relation to endocrine disorders. In: *Cyclopedia of Medicine.* Philadelphia: F. A. Davis Company, 1939. Pp. 543-571.
24. Taylor, H. C., Jr., and Waltman, C. L. Hyperplasias of mammary gland in human being and in mouse: morphologic and etiologic contrasts. *Arch. Surg.* **40**:733-820, 1940.
25. Semb, C. Pathologico-anatomical and clinical investigations of fibroadenomatosis cystica mammae and its relation to other pathological conditions in mammae, especially cancer. *Acta. chir. Scandinav.* **64**: (Supp. 10) 1-484, 1928.
26. Geschickter, C. F. Endocrine aspects of chronic cystic mastitis. *South. Surgeon* **10**:457-486, 1941.
27. Cole, W. H., and Rossiter, L. J. Chronic cystic mastitis: with particular reference to classification. *Ann. Surg.* **119**:573-590, 1944.
28. Warren, S. Relation of "chronic mastitis" to carcinoma of breast. *Surg., Gynec. & Obst.* **71**:257-273, 1940.
29. *Idem.* Prognosis of benign lesions of female breast. *Surgery* **19**:32-39, 1946.
30. Lorie, J. W. Mastopathia cystica and mammary carcinoma. *Cancer Research* **2**:394-397, 1942.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 32401

PRESENTATION OF CASE

A sixty-three-year-old diabetic housewife entered the hospital because of abdominal swelling and pain in the right upper quadrant.

A week before admission the patient first noticed an intermittent pain in the right upper quadrant of the abdomen and occasionally a pain in the right thoracolumbar region. The pain was not influenced by food. The patient felt nauseated at times but did not vomit. The bowels moved daily in a normal fashion, and the stools became light yellow five days before admission. The urine became darker with the onset of this illness. Two days before admission the sugar reaction turned from green to brown. At the onset of the illness the patient noticed that the abdomen was increasing in size. The abdominal pain and swelling progressed gradually until the day of admission, when the pain became much severer. An injection given by a physician gave relief and the abdomen was painless at the time of entry.

The patient had had recognized diabetes for eleven years, during which she was seen frequently in the Out Patient Department. The glycosuria was usually well controlled, but six years before admission one toe became gangrenous and in the following years there were several hospital admissions for gangrene of the toes and suppuration at the sites of amputation. Early in the disease moderately increased deep reflexes of the lower extremities, bilateral Babinski reflexes and partial impairment of position and vibratory sensations were noted. There was no anemia, and the gastric acidity was normal. The last hospital stay, four months previously, had been for cellulitis of the right foot and ankle. The blood pressure had always been in the neighborhood of 190 systolic, 100 diastolic, and moderate cardiac enlargement had been present for several years. Aside from these findings and the infection, the physical examination at the last admission had been negative. The fasting blood sugar was 93 mg. per 100 cc.

Physical examination showed an obese woman in no distress. The pupils were constricted and responded to accommodation, but had a paradoxical reaction to light; on former admissions they had been sluggish, but within normal limits. There were rales at the lung bases. There was a Grade I systolic murmur at the apex and base of the heart. The cardiac rhythm was regular. The abdomen was distended, and a fluid wave was elicited. Tenderness was confined to the right upper quadrant, where it was pronounced. The liver could not be definitely felt but was thought to be enlarged to the crest of the ilium. The tip of the spleen was palpable. The left fourth and fifth toes were missing, and there was a transmetatarsal amputation on the right. The legs were moderately edematous. Neurologic examination was negative.

The temperature was 98°F., the pulse 72, and the respirations 16. The blood pressure was 160 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 11,600, with 82 per cent neutrophils. The urine was yellow and had a specific gravity of 1.015. There was a ++++ test for albumin, a ++ reaction for bile and a green sugar reaction. The sediment contained an occasional white cell per high-power field. The stools, which were tan and formed, gave negative guaiac reactions. The fasting blood sugar was 88 mg. per 100 cc. The bilirubin was 2.2 mg. per 100 cc. direct, and 3.0 mg. indirect. The cephalin-flocculation test was + in twenty-four hours and +++ in forty-eight hours. The total protein was 6.1 gm. per 100 cc., with 4.0 gm. of albumin and 2.1 gm. of globulin. The nonprotein nitrogen level and the prothrombin time were normal. Abundant colon bacilli were cultured from the urine.

A paracentesis on the day after admission yielded 1500 cc. of cloudy, orange-colored fluid with a specific gravity of 1.010. There were 5400 white cells, most of which were neutrophils, and 900 red cells per cubic millimeter. Considerable fluid remained in the abdomen after the tap. The liver could not be palpated. An x-ray film showed the stomach to be distended with air. All abdominal structures were poorly outlined because of fat or fluid, or both. The spleen was slightly enlarged, but the liver shadow was not delineated. On the third day 300 cc. of fluid was removed. Slight but definite icterus of the scleras and skin had appeared. The patient was apathetic and during the following day became confused. Many urine tests for sugar were blue or green, and the highest blood-sugar level was 195 mg. per 100 cc. Forty units of protamine insulin were given daily. The arms and legs became cold and moist. The abdomen remained distended, and the temperature normal.

By the fifth hospital day the patient was not responsible and the jaundice of the scleras had increased. At noon the blood sugar was 261 mg. per 100 cc., and the carbon dioxide 15.8 milliequiv. per liter. Half an hour later she died quietly. At no

time was the pulse, respiration or temperature elevated.

Differential Diagnosis

Dr. Daniel Ellis: I do not believe that the diabetes as such was the cause of the immediate illness and death in this case. In the terminal stage there was acidosis, which I consider to have been due to whatever else the patient had and not to the fact that the diabetes was not well controlled. There is no indication of diabetic coma or diabetic acidosis.

This case, therefore, is primarily that of a woman who was known to have had diabetes, who on previous occasions had had repeated episodes of infection, and who was admitted to the hospital with a history of pain, swelling of the abdomen and increasing jaundice of approximately a week's duration. I still do not know what she had, and my final diagnosis will be given without too much conviction. The best I can do is to mention some of the possibilities.

About 50 per cent of the cases with ascites are on a cardiac basis. This woman had an elevated blood pressure, and probably had essential hypertension. There were rales at the lung bases, but the facts are stressed that at no time was there difficulty in respiration and that the pulse was not elevated or irregular. According to the record the systolic blood pressure was about 30 points below a previous reading. There was no evidence of venous distention at any time. If this patient had had cardiac failure, which might well explain the presumably enlarged liver, the abdominal pain in the region of the liver, the ascites and the edema of the feet, there should have been more evidence of the disease and of the discomfort that goes with heart failure. I cannot conceive of death from cardiac failure with the picture that is outlined here.

Cirrhosis of the liver is a possibility. The patient may have died of liver failure, but I do not believe that it was on the basis of cirrhosis. The only evidence of abnormal liver function is the cephalin-flocculation test. The prothrombin time, the serum protein, the albumin-globulin ratio, the red-cell count and the hemoglobin were normal, and the jaundice was minimal, although it gradually increased in severity. I do not believe that the terminal picture was due to portal cirrhosis or to hepatitis, which would have been an acute and fulminating one, and from the record I do not believe that an acute infectious process involving the entire parenchyma of the liver was present.

Neoplastic disease must be considered, although there is little evidence from the facts at hand. If she had cancer, it must have involved the abdominal viscera, causing obstruction of the portal circulation. Apparently there was no obstructive jaundice, no history of weight loss and no previous history of prolonged symptoms that might be attributed to a malignant neoplasm. The ascites, if caused by cancer, could have been due either to peritoneal seeding or to obstruction of the portal vein or the inferior vena cava.

The question of infection arises. From time to time there was a chronic, suppurating process in the feet. Did the patient have amyloid disease? If the liver was enlarged, the enlargement might have been due to amyloid disease, but the fact that she had ascites to an increasing degree is slightly against it. Amyloid disease might account for the findings in the urine, however. All I can do at the moment is to mention that diagnosis as a possibility.

Could the patient have had tuberculosis? Tuberculous peritonitis might have caused such a picture, although usually with tuberculosis there is evidence of disease elsewhere. Also, the patient would probably have been febrile. The findings in the ascitic fluid are rather against tuberculosis. The fluid in a tuberculous peritonitis usually has a specific gravity of about 1.015, and the cells most frequently found are primarily of lymphocytic origin. Incidentally I should like to check the figures on the fluid. The specific gravity was 1.010, and the white-cell count was 5400. Someone must be wrong.

Dr. Earle M. Chapman: Those are strong words, doctor. That is an important observation in this case. Where is Dr. Averill?

Dr. J. H. Averill: I did the tests, and the figures are correct.

Dr. Ellis: That is all I wanted to know. I must say, then, that the terminal disease was one of intra-abdominal infection. Probably one of the reasons that the first paracentesis yielded only 1500 cc. of fluid is that the abdomen was large and distended and contained fluid that was pocketed; that is only an assumption, however. One might point out that the pain was due to stretching of the liver capsule, which may cause pain and on occasion simulates an acute abdominal emergency. As I mentioned previously, this type of pain, apparently severe enough to require morphine, occurs in right-sided cardiac failure or in an acute hepatitis. Possibly the morphine obscured the findings on admission. One must therefore consider the possibility of a ruptured viscus, obscured by the morphine, although I think that it is unlikely.

So far as the source of infection is concerned, I am driven back to the fact that there were repeated infections in the past, and although I am not sure that such a thing is possible, a pylephlebitis of a septic nature may have occurred from repeated infection in the extremities. Perhaps the most logical diagnoses are a pylephlebitis involving the liver, with septic abscesses, and peritonitis, and the terminal picture was one of overwhelming sepsis to such an extent that there was no rise in pulse rate and no great rise in the white-cell count, although the latter was definitely elevated, with 82 per cent neutrophils. The second choice is tuberculous peritonitis, with the obvious complications of diabetes,

generalized arteriosclerosis and arteriosclerotic heart disease.

DR. WYMAN RICHARDSON: I was going to discard the white-cell count and say that the patient had a pyelonephritis initiated by a renal factor and perhaps a mild portal cirrhosis also in the background.

DR. ELLIS: If a renal condition caused an illness of this degree and death, would not the nonprotein nitrogen have been elevated?

DR. RICHARDSON: Was that determination made?

DR. ELLIS: Yes; the nonprotein nitrogen was normal.

DR. JAMES TOWNSEND: There was only one white cell per high-power field in the sediment. Is that not against pyelonephritis?

DR. RICHARDSON: There were a ++++ test for albumin and abundant colon bacilli.

DR. ELLIS: The albumin is consistent with acute infection elsewhere and dehydration.

DR. BENJAMIN CASTLEMAN: The field is still wide open.

DR. JOHN GRAHAM: I should like to ask Dr. Ellis if he has any opinion about the abnormal neurologic findings.

DR. ELLIS: I could not make much out of them.

DR. GRAHAM: What about the pupillary findings?

DR. ELLIS: The pupillary findings on the last admission, I think, were due to morphine. The previous neurologic findings could be explained on an arteriosclerotic basis.

DR. CHAPMAN: This was indeed a difficult case, and as I listened to Dr. Ellis I could appreciate how he felt. We had a disagreement on the service. There were four possibilities: heart disease, infection, cirrhosis and cancer. We excluded cardiac failure and infection, although we did not seriously entertain massive infection, as Dr. Ellis suggested. We were then left whit cirrhosis and cancer and there we had the disagreement.

My interpretation was that the patient had been diabetic for years and had gone into cholemia. After the paracentesis was done we could not feel a large liver so that I interpreted it as a small, shrunken liver and thought that the cirrhosis had been present for a long time. The fluid was a transudate and not an exudate. The specific gravity was 1.010 and yet the cell count was high. How to explain this was the question. Dr. Averill took the other stand — that it was intra-abdominal cancer, with seeding throughout the peritoneum. He could not explain the low specific gravity any more than I could explain the large number of cells. Then came the point of explaining the urinary albumin. Did the patient have nephritis? I thought that she probably had a hepatorenal syndrome with a failing liver. With destruction of the liver protein massive albuminuria occurs; I should like to refer to an article by Thomas,* who calls attention to the presence of serum protein in the urine as a detoxifying process. In artificial nephritis in dogs Thomas found that liver protein was first excreted and that tissue protein later joined the serum protein and both were excreted. With this mechanism in mind I postulated that the excessive proteins in the urine were liver and not body-tissue proteins.

DR. N. H. MARTIN†: How do you explain the albumin-globulin ratio?

DR. CHAPMAN: I cannot explain it.

DR. MARTIN: In chronic cirrhosis the patient regenerates sufficient tissue to maintain a normal serum protein, but with loss of liver tissue the total protein ultimately drops below the maintenance level. If liver failure is acute there may be a short period when the patient lives on protein "capital," but then a fall in the total protein and a change in the albumin-globulin ratio occur; or death may come before this serum change.

DR. ELLIS: Normal albumin-globulin ratios are frequently encountered in the presence of fatal hepatic damage. Within the last week we have seen a patient who died because of massive destruction of the liver by an infiltrating cancerous process. His death was obviously one of liver failure, and yet the liver-function tests a week before death were normal.

DR. TOWNSEND: Dr. William C. Burrage suggests that this may have been the specific type of cirrhosis that is associated with diabetes — namely, hemochromatosis. Usually these patients have difficulty in controlling the diabetes over a long period. This history does not suggest hemochromatosis to me, but I should like to hear a discussion about that.

DR. CHAPMAN: This woman had the most extraordinary pale, clear-white skin of anyone I have ever seen. We could not possibly entertain that diagnosis. It is true that she was jaundiced, but the jaundice developed only forty-eight hours before death.

DR. TOWNSEND: Was the ascitic fluid examined for tumor cells?

DR. B. J. KENNEDY: Yes; but no tumor cells were found.

CLINICAL DIAGNOSES

Diabetes mellitus.
Cholemia.
Abdominal cancer?

DR. ELLIS'S DIAGNOSES

Pylephlebitis, with multiple abscesses, of liver, portal obstruction and secondary peritonitis.
Generalized arteriosclerosis.
Arteriosclerotic heart disease.
Diabetes mellitus, controlled.

ANATOMICAL DIAGNOSES

Carcinoma of pancreas, with metastases to regional lymph nodes, liver, lungs and pleura.

*Thomas, W. A. Source and role of urinary protein in nephritis. *J. A. M. A.* 97:1055, 1931.

†Of the Middlesex Hospital, London.

Thrombosis of portal vein and right hepatic artery.
Massive infarction of liver, right lobe.
Infarcts of spleen and kidney.
Cardiac hypertrophy, hypertensive type, mild.

Pathological Discussion

Dr. Castleman: Autopsy showed a number of unusual findings. The heart was enlarged, weighing 450 gm. It showed mild hypertensive hypertrophy of the left ventricle. There was no evidence of heart failure. The liver was slightly enlarged, weighing 1800 gm., and presented on the surface a mottled appearance. There were numerous nodules, which seemed to be obviously carcinomatous, studded over its entire surface. They were not raised, as they usually are in carcinoma, but on cutting into them they appeared neoplastic. The liver surrounding the islands of tumor seemed softer and grayer than normal. When the liver was sectioned there was a marked difference between the right and left lobes. There was tumor in both lobes, but the intervening parenchyma in the right was soft and yellowish gray and the markings were completely obliterated; no central veins could be made out, and it had the appearance of a massive infarction. The left lobe showed tumor nodules but without any of the yellowish-gray softening, and the central veins were easily discernible. In the portal vein we found a large thrombus that extended somewhat into the splenic and somewhat into the superior mesenteric vein.

We know that portal-vein thrombosis produces partial infarction of the liver, in which one sees marked acute congestion microscopically but no necrosis of the liver cells to any degree. Ordinarily, when one finds infarction of the liver, one also expects to find a thrombus in the hepatic artery. That was looked for, and in the intrahepatic portion of the main right hepatic artery we found a fresh thrombus, which we believed to account for the complete infarction of the right lobe. There was no thrombus in the left branch. The combination of the portal-vein thrombosis and that of the right hepatic artery was probably responsible for the rapid development of cholemia. The carcinoma itself, I am sure, would not have produced the signs of cholemia. The primary source of the carcinoma was in the head of the pancreas. In addition to the liver there were metastases in most of the regional lymph nodes in the pleura and, on microscopic section, in the lung parenchyma. The source of the hepatic-artery thrombosis is still unsolved. There was a good deal of tumor surrounding the hepatic artery, and quite possibly pressure by the tumor produced thrombosis. Of course it may have been an embolus, and in favor of that theory was the finding of small infarcts in the spleen and kidney; we were unable to find any source in the aorta or heart, however.

Dr. William McK. Jefferies: Do you think that decompression from the abdominal paracentesis could have resulted in portal-vein thrombosis?

Dr. Castleman: I do not believe so. The portal-vein thrombosis was fairly old, not so recent as the hepatic-artery thrombosis. The kidneys showed marked sclerosis, and in a few areas the glomeruli showed the intercapillary glomerulosclerosis that is seen in diabetes.

Dr. Richardson: Was there pyelonephritis?

Dr. Castleman: No. The ascitic fluid, which was a transudate, was not due to neoplastic implants but was the result of the portal-vein thrombosis.

Dr. Ellis: How about the nature of the ascitic fluid? I should like elucidation of these findings, that is, the low specific gravity and the relatively high white-cell count.

Dr. Castleman: I do not know the answer.

Dr. Richardson: Was the specific gravity determined when the fluid was hot or cold?

Dr. Averill: The test was made ten minutes after the tap; the fluid had probably cooled off somewhat.

CASE 32402

Presentation of Case

A fifty-five-year-old Ukrainian-born restaurant porter entered the hospital because of severe hematemesis.

Eight months before admission the patient began to have a mild burning sensation in the epigastrium half an hour after heavy meals. This complaint never caused much distress or required medication. At that time he passed two black stools. A week before admission the burning sensation became worse, but was always relieved by a proprietary preparation containing bismuth. Every day for a week there were one or two loose black stools and the patient was increasingly weak. Six hours before admission on going to bed he felt weak and dizzy. He was awakened two hours later by nausea and vomited a large quantity of bright-red blood and dark clots with considerable violence. He then fainted and was unconscious for several minutes. He subsequently vomited blood once, but less violently. There was never any pain associated with the illness.

The patient had been chronically constipated for years and had lived on a diet of soup, stew and daily laxatives for the seven years before admission.

Physical examination showed the skin to be pale, dry and warm. The tongue was smooth, and the mucous membranes pale. The pulse was strong and regular. The heart, lungs and abdomen were normal, as was peristalsis.

The temperature was 98.6°F., the pulse 80, and the respirations 16. The blood pressure was 118 systolic, 65 diastolic.

Examination of the blood revealed a red-cell count

of 2,750,000, with 8 gm. of hemoglobin, and a white-cell count of 12,500, with 90 per cent neutrophils. The urine was normal. The prothrombin time was 29 seconds (normal, 22 seconds); the nonprotein nitrogen was 47 mg. and the total protein 5.3 gm. per 100 cc. The stools were tarry and gave ++++ guaiac reactions.

Whole-blood transfusions were given for two days, after which x-ray examination of the stomach and duodenum was made. The stomach was normal, but there was a defect in the duodenum that moved with peristalsis and had the appearance of a polyp. By the fifth hospital day the patient's condition was definitely worse despite 1000 cc. of whole blood given daily. There was no more vomiting until the fifth day, but nausea was constant and the stools were always black. On that day the hemoglobin was 8.1 gm. After a transfusion the patient suddenly vomited 300 cc. of blood, the pulse rose to 125, and the systolic pressure fell to 110. The pulse had returned to 100 by the next morning. The prothrombin time was 32 seconds (normal, 20 seconds), and the nonprotein nitrogen 84 mg. per 100 cc. Gastric x-ray studies on the sixth day showed a normal stomach. The filling defect in the duodenum had disappeared and was assumed to have been a blood clot.

An operation was performed on the seventh hospital day.

Differential Diagnosis

Dr. Peter Sarris: This history is rather simple and direct in comparison with most histories that are presented here. It is equally striking by the absence of any positive data on which to make a diagnosis. In this case a diagnosis must be made by exclusion rather than by the more satisfactory method of presenting positive evidence.

Before discussing the differential diagnosis I should like to point out a few things in the history and physical examination. This eight months' story of a mild burning sensation only after heavy meals is not particularly impressive or diagnostic. Many people have a mild burning sensation after a heavy meal, especially if the meal consists of soup, stew and a daily laxative. The symptom is important, however, in view of the fact that it was associated with black stools eight months before admission. Such stools, as information given by a patient, are not always significant. When many leads are traced it is often found that the patient did not have really tarry stools. In this case the statement can be accepted because the patient later had unquestionable melena and was therefore familiar with the appearance of tarry stools. The onset can thus be dated eight months previously, but I do not find any information that helps to make a differential diagnosis. The only helpful point is the massive gastrointestinal hemorrhage. The record mentions vomiting with considerable violence. To me that means that the stomach was probably in good tone and not one of those atonic, dilated, chronically obstructed stomachs with consequent overflow vomiting. It might also mean that the clots produced partial pyloric obstruction. The constipation I cannot tie up with the rest of the story. Once started with cathartics, the patient probably had to stick to them. That, in addition to the diet, may have been significant in producing a vitamin deficiency. I shall return to that later.

The physical examination really contributes nothing except the statement that the patient was anemic, confirming the fact that hemorrhage had occurred, and the history indicates that the patient was not in shock on admission: the pulse was 80, and the blood pressure was satisfactory.

The laboratory data are also of little assistance except to confirm the anemia. The white-cell count and the markedly increased neutrophil count confirm the recent hemorrhage. The urine was normal. I take it that that was an aggregate report. Apparently several examinations were done to exclude any urinary insufficiency or nephritis, which might conceivably tie up with the gastrointestinal bleeding. The prothrombin time was 29 seconds,— later 32 seconds,— which is slightly elevated but not in the range that would explain bleeding from a prolonged prothrombin time per se. The nonprotein nitrogen was 47 mg. and later 84 mg. per 100 cc., which is, of course, definitely abnormal. Anyone with major gastrointestinal bleeding, however, is entitled to it, because not only the accompanying dehydration and the periodic hypotension but also the ingestion of blood itself raise the nonprotein nitrogen, even if the patient has properly functioning kidneys and is otherwise normal. I therefore do not ascribe any particular significance to the high nonprotein nitrogen in this patient.

The course in the hospital suggests little more than that massive bleeding continued. The patient required a transfusion of 1000 cc. of blood daily and after five days of this regime the hemoglobin was the same as it was on the day of admission; presumably, 5000 cc. of blood had been lost in five days.

In this type of bleeding one can dispose of a number of diagnoses because of lack of evidence, such as poisoning and chronic ulceration from tuberculosis or syphilis, although in such conditions massive bleeding sometimes occurs. There is no massive bleeding with uremic ulcers and the acute ulcers that accompany acute infectious disease. Jaundice from any cause may lead to massive hematemesis. Blood dyscrasias such as leukemia and purpura also produce massive bleeding. There is no evidence of blood dyscrasias as from the blood smear, however, and it is unusual for them to cause so much gastric bleeding without evidence of a hemorrhagic tendency somewhere else. These diseases can all be excluded either because of lack of evidence or because the diagnosis can be made only when there is a

specific finding pointing to that diagnosis. The bleeding from a high prothrombin time, which I mentioned earlier, can be excluded since it was not sufficiently high in this case to produce bleeding per se, although it might have contributed to the aggravation of the bleeding. Furthermore, in cases of bleeding due to an elevated prothrombin time, jaundice or sepsis is almost always apparent as the cause.

The source of bleeding can be limited to a location between the lower esophagus and the duodenum. The combination of melena and hematemesis fairly well limits the lesion to that area, which of course is a large area and can include a great deal of disease. In the course of bleeding from duodenal ulcer melena usually precedes hematemesis and often there is only melena, whereas in bleeding from the esophageal varices the reverse is true.

Once in a while one sees massive hemorrhage from a gallstone that has perforated into the duodenum, usually from a gangrenous gall bladder. There was no evidence of gall-bladder disease in this case, and certainly such an episode of perforation into the duodenum would have been accompanied by pain, which was absent. In such cases, the bleeding is incidental.

One more cause, idiopathic bleeding, when nothing else is found, can be excluded. In some patients with repeated and marked bleeding even after part of the stomach is resected the bleeding continues and no explanation is ever found. I do not believe that that is the answer in this case. Presumably, Dr. Mallory will confront us with some pathologic lesion. Cancer, peptic ulcer, esophageal and gastric varices, gastritis and benign gastric tumors remain.

It might be wise to see the x-ray films at this point.

Dr. Milford D. Schulz: The x-ray films taken in this case are missing.

Dr. Sarris: I think it fair to ask, then, if the roentgenologist was satisfied with the second film showing a completely normal stomach and duodenum, excluding the possibility suggested by the first film of a polyp that might have receded into the fundus of the stomach and therefore become invisible.

Dr. Schulz: That is a possibility, of course, but the fact that the disappearing lesion was assumed to be a blood clot indicates a careful search for some explanation.

Dr. Lewis K. Dahl: I might amplify Dr. Schulz's remark by saying that Dr. Schatzki considered his examination to be reasonably satisfactory.

Dr. Sarris: I take it that gastroscopy was not done and that it was regarded as inadvisable.

Dr. Tracy B. Mallory: I believe that that is true.

Dr. Sarris: I also take it that no cellular studies were made on the gastric contents. Such studies are becoming increasingly valuable for early diagnosis.

Dr. Mallory: No such information is given.

Dr. Sarris: I believe that gastric cancer is the least likely diagnosis. First of all, it accounts for only 5 per cent of the massive hemorrhages, and there was no suggestive history; there was no weight loss, and no weakness except after massive bleeding. Furthermore, I believe that a gastric cancer is not likely to have been missed by x-ray examination.

Peptic ulcer must be more seriously considered because it accounts for 75 per cent of massive hemorrhages of this type. The history is reasonably consistent with it, although the burning sensation was mild only after heavy meals. I do not recall seeing such a massive hemorrhage from duodenal ulcer in which some deformity of the duodenum — a crater, spasm or a similar lesion — was not demonstrated by x-ray examination. This patient had two examinations. The lesion could have been a small peptic ulcer in the stomach, which is sometimes missed in the x-ray film.

Esophageal varices, which account for 5 to 10 per cent of massive hemorrhages of this type, are secondary to cirrhosis, hepatic insufficiency or previous portal or splenic thrombosis. Many patients enter the hospital for the first time because of massive bleeding from esophageal varices, and the diagnosis of portal cirrhosis is made. Usually, some abnormality, such as an enlarged spleen, is disclosed by the physical examination or by laboratory tests, such as liver-function studies, which were not done in this case. The most important feature against esophageal varices is the x-ray film, which rarely misses them. Gastric varices offer a different problem, since they can be missed by x-ray examination. I remember a case with repeated hematemesis in which several x-ray films were taken and nothing was demonstrated. At operation, performed with Dr. Richard H. Sweet, the patient was found to have varices limited to the fundus. Gastric varices must therefore be considered, but there is no evidence for the disease that produced the varices. Gastritis, with single or multiple erosions, which has been encountered in several cases, could well have been present, the erosions being superficial and peptic in nature but not deep enough to produce a lesion visible on x-ray study.

The last consideration is benign gastric tumor, which includes adenoma, leiomyoma, hemangioma, neurogenic fibromas and lipoma. Excessive bleeding is characteristic of such tumors, particularly the adenomas, the leiomyomas and the hemangiomas. They may be pedunculated, and when I first read this history, before I reached the last paragraph, it seemed certain that the diagnosis was an adenoma that had prolapsed into the duodenum. That is why I was anxious to determine the possibility of a polyp. But the roentgenologists apparently believed that the possibility of a polyp that receded into an invisible position was much less than that of a blood clot. Therefore, if this was a benign tumor of the stomach, there was no conclusive x-ray evidence.

In conclusion the diagnosis depends on the consideration of which lesion that I have mentioned is not only frequent enough to be considered but also likeliest to be missed by x-ray examination. Benign tumors are often overlooked unless they are large or have a large ulceration, which they sometimes do. If the tumors are small and are not deeply ulcerated they are missed because they do not disturb peristalsis and do not usually produce spasm and because the mucosal pattern is often normal. I cannot make any final decision. If it turns out to have been a benign tumor, the adenomas and leiomyomas are of the commonest occurrence. The bleeding tumors most frequently encountered are the hemangiomas and the adenomas, which are my first choice. My second choice is a gastritis, with single or multiple superficial erosions. My third choice is gastric varices.

DR. EDWARD B. BENEDICT: Nine times out of ten, in massive hematemesis, one would be correct in saying that the lesion was a benign peptic ulcer. I cannot quite agree with Dr. Sarris about the x-ray finding. I can recall 3 cases within a few years with massive hematemesis in which, in spite of an entirely negative x-ray examination, benign peptic ulcers were present.

DR. SARRIS: In the stomach?

DR. BENEDICT: Yes; in the stomach. In 1 case, in which the ulcer was prepyloric, gastroscopy demonstrated nothing. Another ulcer was in the upper part of the stomach, and the patient was not gastroscoped. The third was in the midpart, and gastroscopy a month before operation showed gastritis but did not show the tiny ulcer that was bleeding.

DR. SARRIS: The point that Dr. Benedict has made is well taken. I included a small benign peptic ulcer with the diagnosis of gastritis with single or multiple superficial erosions, because the small benign gastric peptic ulcers are to me similar to the superficial erosions in some cases of gastritis. Both conditions are often missed by x-ray examination.

CLINICAL DIAGNOSIS

Leiomyoma of stomach.

DR. SARRIS'S DIAGNOSIS

Benign gastric tumor.

ANATOMICAL DIAGNOSIS

Cirsoid aneurysm of left gastric artery, with secondary peptic erosion.

PATHOLOGICAL DISCUSSION

DR. MALLORY: We hardly expected Dr. Sarris to make the diagnosis because this case presented a lesion that is unique in the experience of this laboratory.

Will you tell what you found at operation, Dr. Hamlin?

DR. EDWARD HAMLIN, JR.: On opening the abdomen we found the upper gastrointestinal tract filled with blood and nothing else. We thought seriously for a time that we were dealing with idiopathic bleeding, which Dr. Sarris mentioned. The third part of the duodenum and the stomach were carefully inspected. We opened the stomach along the antrum and found a great deal of blood and nothing else. While we were cogitating — the stomach was suspended between forceps — we noted blood accumulating in the upper part of the stomach, and that limited the field. Going over it carefully again we found a minute, actively bleeding speck, which was partially blood clot, about two thirds of the way from the pylorus to the fundus on the posterior wall. This was resected.

FIGURE 1. *Photomicrograph of the Large Eroded Vessel in the Submucosa, with Thrombus Formation.*

DR. MALLORY: The gross specimen that we received showed a small projecting red mass, which was evidently a thrombus overlying an artery in the submucosa. On dissecting the specimen further it was evident that an unusually large branch of the left gastric artery — as large as the main artery itself — came up through the muscularis into the mucosa for a distance of perhaps 0.5 cm. and then turned around and bent down again to penetrate the muscularis once more. This vessel was sclerotic and tortuous, and we classified it as a cirsoid aneurysm. The mucosa over the artery and one side of its wall were entirely eroded away (Fig. 1). I suppose that the pressure of this abnormally large vessel immediately beneath the mucosa had led to ulceration of the mucosa, peptic in character, with the subsequent massive hemorrhage.

Whether this represents a congenital abnormality of the vessel or a developmental one I do not know any way of determining.

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REALISM VERSUS WISHFUL THINKING

Organized medicine in this country has become increasingly conscious that a large section of the public holds it in low regard. This has been a disturbing thought to the leaders in the profession, as well as to the rank and file, and the average physician is apt to inquire why it is that, although as an individual he seems to be well thought of by those he serves, his collective acts, as expressed through the organizations that he and his colleagues comprise, are held in such low esteem. Is the physician a dual personality — a sort of Dr. Jekyll when serving the public in his individual capacity and Mr. Hyde when he acts in concert with his fellows?

Has organized medicine lost its democratic character? As a matter of fact, the pattern of democracy nowhere in this country is more closely followed than it is in the conduct of the business of the majority of medical societies. Who can truthfully say that the House of Delegates of the American Medical Association is not conceived in the democratic spirit, either in its formation, in the methods attending its deliberations or in the conclusions it arrives at? If this body does not follow the democratic plan neither then does the Congress of the United States, after which it was and continues to be closely patterned.

Can it be said that the democratic process has ceased to function in the Massachusetts Medical Society? Here, again, over the years democracy has grown and expanded. As an example, three of its most important committees — the Committee on Public Relations, the Committee on Legislation and the Executive Committee of the Council — are composed of a representative of each of our eighteen district societies. It may well be that the apparent ill repute of the Society in the minds of the public is conditioned by the indifference that some physicians show toward the conduct of the Society's affairs. This does not, however, connote a real lack of support any more than does the average citizen's attitude of indifference to the actual management of his government.

There seems to be little to support the dual-personality theory. Nor does it seem likely that organized medicine has fallen in esteem because the public believes that it has ceased to walk in the democratic way.

At a meeting of the House of Delegates of the American Medical Association held in July at San Francisco, the delegates were informed of a particular activity that had been conducted under the auspices of the Board of Trustees, which took notice of the suspicions regarding public relations. A firm prominent and skilled in determining public opinion was engaged to determine whether these suspicions had any foundation in fact and if so what was to be done about it. On the one hand, this effort confirmed the popularity of the individual physician, and on the other, the low esteem in which he and his fellows are held as an organized group.

In an endeavor to find the answer to what seemed like a contradiction, those making the survey examined the entire setup of the American Medical Association. They found in the various scientific

activities of the organization so much in the interest of the public good as to constitute a veritable gold mine from the standpoint of public relations. But they also learned that the public knew nothing about such treasure. Most people had heard of the American Medical Association, but principally as an organization that was working for the defeat of such legislation as the Wagner–Murray–Dingell Bill.

The advice looking toward the remedy of this situation was simple. The people should be told about these scientific activities, all of which are so definitely in their interest. They should be told in a language that is easily understood, they should be told at times that are opportune, and they should be told often. It should, however, be recognized that, although this remedy is simple, its proper application requires the services of a person with special experience and skill and that the job will be well done in proportion to the training and ability of the person selected to do it.

The program thus outlined was adopted by the House of Delegates. Whoever is chosen to carry out the plan will work in close harmony with the secretary and the general manager of the American Medical Association and with all its various bureaus and councils.

This is an experiment that offers much promise. It is realism as opposed to wishful thinking; it properly recognizes the value of a well informed public — an asset that has been developed by many organizations during the past ten or twenty years. State medical societies should watch this experiment closely, for in its operation may be found the answer to certain of their own difficulties.

TOXICITY OF TRIDIONE

Infectious diseases are not the only ones that benefit from chemical research. Even the Hippocratic disease, epilepsy, profits from the synthesis of new compounds. Latest encouragement comes from the use of a drug, 3,5,5–trimethyloxazolidine–2,4 dione, the trade name of which is Tridione. The therapeutic peculiarity of this chemical is its nearly specific effect on a particular group of seizures, the so-called "petit-mal triad" — petit mal, akinetic seizures and myoclonic jerks. In one group of 166 patients treated at the Children's Hospital in Boston, two thirds were freed or almost freed of this particular type of seizure. Grand-mal seizures, on the other hand, were not helped and often became more frequent. Because the drug is of specific value for clinical syndromes associated with the alternate spike and wave of the electroencephalogram, it offers intriguing opportunity for further studies.

The more high-powered the weapon of offense, the greater the possibilities of harm if it should backfire. Peculiar reactions may accompany the use of Tridione. Generalized skin rashes are frequent but do not become serious if the drug is discontinued promptly and reinstated gradually. Photophobia (hemeralopia) is a peculiar, but apparently harmless, side effect for which there is as yet no explanation. A more disquieting complication is the occasional appearance of blood dyscrasias. Symptomless leukopenia or eosinophilia has been noted in a few patients,[1] and in two cases recently reported there was aplastic anemia with agranulocytosis, uncontrollable bleeding and death.[2, 3]

An allergic or toxic reaction of a patient to a given drug is always a lively possibility. Withholding medicines that have ever caused serious reactions would work misfortune on the many who require those medicines. Tridione medication has resulted fatally for only one of some 5000 patients being treated. This ratio can be increased if physicians, forewarned, will take the necessary precautions. These are as follows: prescribe Tridione only for the type of seizure that can be helped, — namely, petit mal (pykno-epilepsy), myoclonic jerks and akinetic seizures, — and for patients without a history of blood dyscrasia; give no more than the amount needed to control petit mal; inquire for weakness, pallor, dyspnea, undue bleeding and hemorrhagic skin eruptions; and examine the blood monthly and stop medication if the platelets are substantially reduced, if the white-cell count falls below 4000 or the percentage of neutrophils below 50 per cent or if there is pronounced anemia. Having taken these precautions, the physician can give tridione to his young patients who are subject to petit mal with the expectation that approximately two thirds of them will receive substantial relief from this type of seizures.

References

1. Correspondence. Greaves, R. J. Sensitivity to Tridione. *J. A. M. A.* **132**:44, 1946.
2. Harrison, F. F., Johnson, R. D., and Ayer, D. Fatal aplastic anemia following use of Tridione and hydantoin. *J. A. M. A.* **132**:11-13, 1946.
3. Mackay, R. P., and Gottstein, W. K. Aplastic anemia and agranulocytosis following Tridione. *J. A. M. A.* **132**:13-16, 1946.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

ALMY — Thomas Almy, M.D., died September 6. He was in his sixty-third year.

Dr. Almy received his degree from Harvard Medical School in 1909. He was formerly chief of the staff of Union Hospital, and was a member of the New England Obstetrical and Gynecological Society and the New England Pediatric Society and a fellow of the American Medical Association. He was a diplomate of the American Board of Obstetrics and Gynecology.

His widow survives.

BAILEY — Marshall H. Bailey, M.D., of Norwell, died September 18. He was in his eighty-eighth year.

Dr. Bailey received his degree from the College of Physicians and Surgeons, Baltimore, in 1893.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1946

Résumé

Diseases	August 1946	August 1945	Seven-Year Median
Anterior poliomyelitis	62	127	24
Chancroid	0	1	*
Chicken pox	123	121	121
Diphtheria	20	11	11
Dog bite	1045	974	1031
Dysentery, bacillary	1	54	15
German measles	46	38	38
Gonorrhea	365	459	426
Granuloma inguinale	1	0	*
Lymphogranuloma venereum	0	1	*
Malaria	16	68	6
Measles	400	274	281
Meningitis, meningococcal	4	6	6
Meningitis, Pfeiffer-bacillus	2	1	1
Meningitis, pneumococcal	0	1	1†
Meningitis, staphylococcal	0	2	1†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	2	4	1†
Meningitis, undetermined	3	1	4†
Mumps	142	312	271
Pneumonia, lobar	29	93	77
Salmonella infections	45	48	22
Scarlet fever	112	157	195
Syphilis	310	293	354
Tuberculosis, pulmonary	246	215	260
Tuberculosis, other forms	19	12	23
Typhoid fever	6	4	8
Undulant fever	6	5	5
Whooping cough	498	531	508

*Made reportable December, 1943.

†Four-year average.

Comment

Diseases reported at an incidence above the seven-year median included anterior poliomyelitis, diphtheria, German measles and measles.

Although above median prevalence, poliomyelitis had an incidence of about half that of last year.

Diphtheria showed the highest August prevalence of the last ten years. This is the fourth consecutive month in which such an increase has taken place.

Diseases reported below the median prevalence included meningococcal meningitis, mumps, scarlet fever and whooping cough.

Lobar pneumonia was again at a record low for the seventh consecutive month.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Arlington, 1; Auburn, 1; Beverly, 1; Blackstone, 1; Blandford, 1; Boston, 5; Brookfield, 3; Carlisle, 1; Dedham, 1; Framingham, 1; Franklin, 1; Harwich, 1; Holyoke, 1; Hull, 1; Lancaster, 1; Lowell, 3; Lynn, 1; Lynnfield, 1; Malden, 2; Marblehead, 1; Medford, 1; Methuen, 1; Middleboro, 1; New Bedford, 1; North Adams, 1; North Attleboro, 2; Northampton, 3; Norwood, 1; South Hadley, 1; Somerville, 1; Walpole, 1; Washington, 1; Watertown, 2; Wellesley, 1; Weston, 1; Worcester, 13; Wrentham, 1; total, 62.

Diphtheria was reported from: Boston, 10; Braintree, 1; Cambridge, 1; Mansfield, 1; New Bedford, 2; Somerville, 3; Sudbury, 1; Waltham, 1; total, 20.

Dysentery, amebic, was reported from: Quincy, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 1; total, 1.

Lymphocytic choriomeningitis was reported from: Agawam, 1; total, 1.

Malaria was reported from: Boston, 7; Bourne, 2; Cambridge, 2; Clinton, 1; Haverhill, 1; New Bedford, 1; Oxford, 1; Somerville, 1; total, 16.

Meningitis, meningococcal, was reported from: Boston, 2; Canton, 1; Lawrence, 1; total, 4.

Meningitis, Pfeiffer-bacillus, was reported from: Beverly, 1; Medford, 1; total, 2.

Meningitis, other forms, was reported from: Springfield, 2; total, 2.

Meningitis, undetermined, was reported from: Amesbury, 1; Salem, 1; Shrewsbury, 1; total, 3.

Rocky Mountain spotted fever was reported from: Dennis, 1; total, 1.

Salmonella infections were reported from: Beverly, 3; Boston, 2; Chelsea, 1; Lawrence, 1; Lynn, 23; Malden, 1; Marblehead, 5; Newton, 2; Peabody, 1; Quincy, 1; Springfield, 1; Swampscott, 1; Topsfield, 1; Winchester, 1; Yarmouth, 1; total, 45.

Septic sore throat was reported from: Boston, 7; Brookline, 1; Greenfield, 1; Holbrook, 1; Newburyport, 1; Somerville, 1; total, 12.

Tetanus was reported from: Quincy, 1; total, 1.

Trichinosis was reported from: Boston, 2; Norwood, 1; total, 3.

Typhoid fever was reported from: Boston, 2; Chicopee, 2; Marblehead, 1; Randolph, 1; total, 6.

Typhus fever was reported from: Malden, 1; total, 1.

Undulant fever was reported from: Adams, 1; Dighton, 1; New Ashford, 1; Southbridge, 1; Westminster, 1; Worcester, 1; total, 6.

BOOK REVIEWS

Anatomy as a Basis for Medical and Dental Practice. By Donald Mainland, M.B., Ch.B., D.Sc., F.R.S.E., F.R.S.C. 8°, cloth, 863 pp., with 61 illustrations and 11 tables. New York: Paul B. Hoeber, Incorporated, 1945. $7.50.

It is refreshing to read a textbook of anatomy, such as this, written in a manner that retreats from the conventional method of presentation. Students of medicine and dentistry will find a copy of this book an asset throughout their professional career. A student, soon to begin a course in anatomy, will find himself well oriented in this subject matter if he carefully reads and perhaps rereads Part I, which succinctly discusses the aims and methods of anatomic studies, and then turns to Appendix III, to become acquainted with important hints on how to read and write articles pertaining to anatomy. Armed with the understanding that these chapters will supply, the student is led to the study of Part II, presenting general anatomy, which begins with a considera-

tion of the body as a whole and proceeds to the discussion of bones, joints, muscles and fascias, blood and lymphatic vessels, nerves, skin and appendages. Part III concerns regional anatomy: the upper and lower limbs, thorax, abdomen, head and neck, back, brain and spinal cord and the autonomic nervous system. The reviewer wishes to draw special attention to the appendixes, which deal with subjects such as radiology, postnatal ossification of limbs, normal weights of organs, tooth eruption dates, adult pelvic dimensions and segmental cutaneous nerve supply. Excellent references are given for each chapter, and a good index is supplied.

The volume as a whole has much merit, and the author succeeds in offering his readers a well written, instructive and provocative book.

The Autobiography of Science. Edited by Forest R. Moulton, Ph.D., Sc.D.; and Justus J. Schifferes. 8°, cloth, 666 pp. Garden City, New York: Doubleday, Doran and Company, Incorporated, 1945. $4.00.

It may be said that science had its beginnings in the recording of astronomical observations in Babylonian times, twenty centuries before the beginning of the Christian Era, and that its development has been international in scope, embracing all peoples and languages.

The compilers of this autobiography of science have brought together selections of all countries and all times — from the hieroglyphics of the ancient Egyptians and the *Old Testament* story of the Creation to the modern period of Osler, Cannon and Cushing. The book is fundamentally an anthology of the key passages from the master works of all sciences.

From an original list of three hundred authorities it was found necessary, because of space limitation, to reduce the number to a hundred, and in so doing the compilers were guided by two criteria: their importance as turning points in the history of science and their readability. They also attempted to determine the best thing a person ever wrote about the most important thing he or she ever did, the greatest consideration being given to persons whose work seemed to chart the main stream of the development of scientific thought. Three of the authors quoted are women: Lady Mary Wortley Montagu, Florence Nightingale and Madame Curie. The selections are in general arranged in chronological order by periods under eight headings, beginning with "Science Is Born (Antiquity)" and concluding with "Science Sires the Twentieth Century."

The original texts of fifty-five of the selections, which were in a language other than English, are presented in translations by modern scholars, with the single exception of Cuvier, of whose work a new translation is offered. For the most part the writings are in simple words, easy to understand and to follow in their context. Only eleven of the scientists quoted write in a manner that is slow or hard to read. It is the impression of the compilers that there are fewer than a hundred unusual scientific words among the more than two hundred and fifty thousand words comprising the volume. In only one instance, Einstein, was it considered necessary to provide a special vocabulary.

In preparing the texts for publication the general reader has been kept in mind rather than the specialist, and the final editing has been done in the style of the best current American usage. Mathematical notation and symbolism have been omitted, but mathematical reasoning and theory necessary to the theme have been included.

The selections of each author quoted are preceded by a short biographic commentary.

Of the selections, fifty are on biologic and medical subjects, and of this number thirty-four are medical or of medical interest. The second selection quoted comprises excerpts from the Egyptian, Edwin Smith and Ebers papyri. The second to the last selection is Harvey Cushing's noted "Homo Chirurgicus," which is given in full. The medical selections are all from outstanding, well known names in medicine: Hippocrates and Galen in antiquity; Gui de Chauliac and the Regimen Sanitatis of Salerno in the Middle Ages; Leonardo da Vinci, Paracelsus, Fracastorius, Paré, Vesalius and Harvey in the Renaissance; Leeuwenhoek and Fauchard, the dentist, in the seventeenth and early eighteenth centuries; and Benjamin Franklin, Lady Montagu, Jenner, Laennec, John Snow, Beaumont, Holmes, Crawford Long, W. T. G. Morton Pasteur, Lister, Florence Nightingale, Sedgwick, Roentgen, Freud, Osler, Cannon and Cushing in the later years.

This book may be used as a reference and source book, as a narrative or as a textbook on the history of science. It should be in all libraries, public and private, general and special, and is especially recommended for all medical libraries and for all persons interested in the history of medicine.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Way of an Investigator: A scientist's experiences in medical research. By Walter B. Cannon, M.D. 8°, cloth. 229 pp. New York: W. W. Norton and Company, Incorporated, 1945. $3.00.

The late Dr. Cannon, in this semipopular book, has written an autobiographical account of his work and at the same time has given a description of how the scientific investigator goes about doing his job.

Pulmonary Edema and Inflammation: An analysis of processes involved in the formation and removal of pulmonary transudates and exudates. By Cecil K. Drinker, M.D., D.Sc., professor of physiology, School of Public Health, Harvard University, Boston. The Nathalie Gray Bernard Lectures delivered at the Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina, in December, 1944, together with a fifth chapter on artificial respiration. Monograph No. 7, Harvard University Monographs in Medicine and Public Health. 8°, cloth, 106 pp., with 27 illustrations. Cambridge: Harvard University Press, 1945. $2.50.

Dr. Drinker analyzes the formation and removal of pulmonary transudates and exudates. He also discusses the prevention and treatment of lung edema, and in the final chapter he reviews the problems and technics of artificial respiration.

The Bacterial Cell: In its relation to problems of virulence, immunity and chemotherapy. By René J. Dubos, George Fabyan Professor of Comparative Pathology and professor of tropical medicine, School of Medicine and School of Public Health, Harvard University, and member of the Rockefeller Institute. With an addendum by C. F. Robinow, Strangeways Laboratory, Cambridge, England. Monograph No. 6, Harvard University Monographs in Medicine and Public Health. 8°, cloth, 460 pp., illustrated. Cambridge: Harvard University Press, 1945. $5.00.

This important book describes the organization of the structural and physiologic components of the bacterial cells and interprets the phenomena of virulence, immunity and chemotherapy in terms of cellular organization. The present study utilizes not only direct microscopic methods but also the information derived from indirect methods, based on the physicochemical, physiologic and immunologic behavior of bacteria. This monograph should be in all medical and biologic libraries. An extensive bibliography is appended to the text.

Physical Chemistry of Cells and Tissues. By Rudolf Höber, University of Pennsylvania School of Medicine. With the collaboration of David I. Hitchcock, Laboratory of Physiology, Yale University School of Medicine; J. B. Bateman, Mayo Clinic; David R. Goddard, University of Rochester Biological Laboratories; and Wallace O. Fenn, University of Rochester School of Medicine and Dentistry. 8°, cloth, 676 pp. Philadelphia: The Blakiston Company, 1945. $9.00.

This comprehensive monograph is divided into eight principal sections. The first is devoted to a discussion of selected principles of physical chemistry applicable to the study of cell physiology. Then follow sections on the molecule, protoplast, cellular activity, respiration, contractility, passive penetration and active transfer in animal and plant tissues. The work is well documented, with selected references to the subject, and has adequate author and subject indexes. This monograph should be in all medical and related libraries.

A Manual of Surgical Anatomy. By Tom Jones and W. C. Shepard. Prepared under the auspices of the Committee on Surgery. Division of Medical Sciences, National Research Council. 4°, cloth, 195 pp., illustrated. Philadelphia and London: W. B. Saunders Company, 1945. $5.00.

This latest of the series of military surgical manuals is without text and has been prepared especially for surgeons in the field.

Clinical Biochemistry. By Abraham Cantarow, M.D., professor of physiological chemistry, Jefferson Medical College; and Max Trumper, Ph.D., Lt. Commander, H(S)USNR, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland. Third edition, revised. 8°, cloth, 647 pp., with 29 illustrations. Philadelphia and London: W. B. Saunders Company, 1945. $6.50.

This authoritative textbook has been thoroughly revised to incorporate the progress in biochemistry during the five years that have elapsed since the publication of the second edition. The volume considers many new tests and new subjects, including classifications of jaundice, physiology of gastric and pancreatic secretion and methods for the study of deficiency in the various vitamins; a chapter dealing with hormone assay and endocrine function has been added. The authors have attempted to present controversial subjects in an impartial manner, supplemented by an expression of personal opinion. The last chapter constitutes an outline of chemical abnormalities in various disorders, with pertinent page references. A comprehensive index concludes the volume. Selective bibliographies are attached to each chapter. The material is well organized, and this book should prove valuable for reference purposes.

NOTICES

ANNOUNCEMENTS

Dr. Thomas W. Botsford announces the opening of his office for the practice of general and pediatric surgery at 1101 Beacon Street, Brookline.

Dr. Donald T. Chamberlin announces the opening of his office at 422 Beacon Street, Boston, for the practice of diseases of the digestive system.

Dr. Frederick C. Irving announces the removal of his office to 1180 Beacon Street, Brookline.

Dr. John Ellis Knight announces his return from service with the armed forces and the reopening of his office at 520 Commonwealth Avenue, Boston.

Dr. L. Tillman McDaniel announces his return to the practice of internal medicine at 12 Bay State Road, Boston.

Dr. James F. McDonough announces the opening of his offices for the practice of obstetrics and female diseases at 15 Dix Street, Winchester, and 1101 Beacon Street, Brookline.

Dr. Elsie S. Neustadt announces the opening of an office for the practice of psychiatry and neurology at 27 Avon Way, Quincy.

Dr. Ian P. Rak announces his return to the practice of psychiatry and neurology at 422 Beacon Street, Boston.

Dr. Eugene Suzedell announces his return from military service and resumption of practice at 59 Coddington Street, Quincy.

Dr. Aldo G. Verde, having returned from service with the United States Navy, announces the opening of his office for the general practice of medicine and surgery at 676 Adams Street, Dorchester.

VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Provided essays of sufficient merit are presented in competition, the award will be made at the annual meeting of the association, which will be held in Atlanta, Georgia, on April 3, 4 and 5, 1947.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English; a typewritten double-spaced copy should be sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors' Building, Atlanta 3, Georgia, not later than January 1, 1947. The committee that will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the *Proceedings* of the association. This will not prevent its further publication, however, in any journal selected by the author.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, October 4 — Aggressive Behavior — Its Psychiatric and Physiologic Aspects, Especially in Combat Veterans. Dr. Leo Alexander.

Wednesday, October 9 — Iodine Metabolism. Dr. John VanderLaan.

Friday, October 11 — Hepatic Function with Respect to Bromsulphalein Removal. Dr. Franz J. Ingelfinger.

Wednesday, October 16 — Tuberculous Lesions of Bones and Joints. Dr. Arthur A. Thibodeau.

Friday, October 18 — Recent Studies in Hemorrhagic Shock. Dr. Arnold M. Seligman.

Wednesday, October 23 — Massachusetts Medical Society. Dr. Dwight O'Hara.

Friday, October 25 — Pituitary Adrenal Relations. Dr. R. O. Greep.

Wednesday, October 30 — Homologous Serum Hepatitis. Dr. William Maloney.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each week day by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The annual meeting of the New England Obstetrical and Gynecological Society will be held in Boston on Wednesday, October 30, with headquarters at the Hotel Somerset.

NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The regular fall meeting of the New England Oto-Laryngological Society will be held in conjunction with the Massachusetts Eye and Ear Alumni on Wednesday, November 20, at 11 a.m. at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston.

(*Notices continued on page xii*)